VA/DOD Evidence-Based Clinical Practice Guidelines
Opioid Therapy for Chronic Pain
Follow-Up Call with Work Group – January 30, 2017
11:30 AM - 12:30 PM ET

SUMMARY

Participants:

VA: (b)(6)
DoD: (b)(6)
Champions: (b)(6)
Work Group: (b)(6)
(b)(6)
The Lewin Group: (b)(6) (Facilitator)
Sigma Health Consulting: (b)(6)
ECRI Institute: (b)(6)
Duty First Consulting: (b)(6)

This document provides a summary of key discussion points from the conference call with the Champions, Work Group, VA and DoD Leadership, and the Lewin Team. An agenda and a summary of the previous call were distributed in advance of the call. The discussion topics were

Meeting Overview

- **Administration:**
  - Lewin provided a brief overview of the previous call.
- (b)(5)
- **Next Steps:**

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Withheld pursuant to exemption

(b)(6) ; (b)(5)

of the Freedom of Information

Page 3 of 6

Withheld pursuant to exemption

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of the Freedom of Information

(b)(5); (b)(6)

(b)(5); (b)(6)

(b)(5); (b)(6)

Next Steps

(b)(5)

VA/DoD CLINICAL PRACTICE GUIDELINE FOR OPIOID THERAPY FOR CHRONIC PAIN

Department of Veterans Affairs

Department of Defense

QUALIFYING STATEMENTS

The Department of Veterans Affairs and the Department of Defense guidelines are based upon the best information available at the time of publication. They are designed to provide information and assist decision making. They are not intended to define a standard of care and should not be construed as one. Neither should they be interpreted as prescribing an exclusive course of management.

This Clinical Practice Guideline is based on a systematic review of both clinical and epidemiological evidence. Developed by a panel of multidisciplinary experts, it provides a clear explanation of the logical relationships between various care options and health outcomes while rating both the quality of the evidence and the strength of the recommendation.

Variations in practice will inevitably and appropriately occur when clinicians take into account the needs of individual patients, available resources, and limitations unique to an institution or type of practice. Every healthcare professional making use of these guidelines is responsible for evaluating the appropriateness of applying them in the setting of any particular clinical situation.

These guidelines are not intended to represent TRICARE policy. Further, inclusion of recommendations for specific testing and/or therapeutic interventions within these guidelines does not guarantee coverage of civilian sector care. Additional information on current TRICARE benefits may be found at www.tricare.mil or by contacting your regional TRICARE Managed Care Support Contractor.

Version 3.0 – 2017

Prepared by:

The Opioid Therapy for Chronic Pain Work Group

With support from:

The Office of Quality, Safety and Value, VA, Washington, DC
&
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Version 3.0 – 2017

Based on evidence reviewed through December 2016

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I. Introduction

The Department of Veterans Affairs (VA) and Department of Defense (DoD) Evidence-Based Practice Work Group (EBPWG) was established and first chartered in 2004, with a mission to advise the "…Health Executive Council on the use of clinical and epidemiological evidence to improve the health of the population across the Veterans Health Administration and Military Health System," by facilitating the development of clinical practice guidelines (CPGs) for the VA and DoD populations.[1] This CPG is intended to provide healthcare providers with a framework by which to evaluate, treat, and manage the individual needs and preferences of patients with chronic pain who are on or being considered for long-term opioid therapy (LOT).

In 2010, the VA and DoD published the *Clinical Practice Guideline for Management of Opioid Therapy for Chronic Pain* (2010 OT CPG), which was based on evidence reviewed through March 2009. Since the release of that guideline, there has been growing recognition of an epidemic of opioid misuse and opioid use disorder (OUD) in America, including among America's Veterans, as documented in the Background section. At the same time, there is a mounting body of research expanding detailing the lack of benefit and severe harms of LOT.

Consequently, a recommendation to update the 2010 OT CPG was initiated in 2015. The updated CPG, titled *Clinical Practice Guideline for Opioid Therapy for Chronic Pain* (OT CPG), includes objective, evidence-based information on the management of chronic pain. It is intended to assist healthcare providers in all aspects of patient care, including, but not limited to, diagnosis, treatment, and follow-up. The system-wide goal of this guideline is to improve the patient's health and well-being by providing evidence-based guidance to providers who are taking care of patients on or being considered for LOT. The expected outcome of successful implementation of this guideline is to:

- Assess the patient's condition, provide education, and determine the best treatment methods in collaboration with the patient and a multidisciplinary care team
- Optimize the patient's health outcomes and function and improve quality of life
- Minimize preventable complications and morbidity
- Emphasize the use of patient-centered care

II. How to Use This Clinical Practice Guideline

This guideline can be used in a variety of ways. It can be used by general clinicians or specialists to study and consider the latest information on opioid therapy (OT) and how and whether to incorporate that information or recommendations into their practice. It can be used to provide specific information to guide a patient encounter, such as looking up the dosing of a medication used less frequently or the meaning of the urine drug testing (UDT) result. The section on tapering and its accompanying appendix can be used to assist in the development of a framework for guiding an individualized, informed discussion when tapering is being considered. Patients can examine the guideline to educate themselves and better understand their care. A health care system can use the CPG to assure that its clinicians and patients have the resources available to compassionately, effectively, and safely evaluate and deliver LOT in a timely, culturally sensitive manner. The guideline can also be used to suggest specific education for identified gaps.

This guideline is not intended as a standard of care and should not be used as such. Standards of care are determined on the basis of all clinical data available for an individual case and are subject to change as scientific knowledge and technology advances and patterns evolve. Today there is variation among state regulations, and this guideline does not cover the variety of ever-changing state regulations that may be pertinent. The ultimate judgement regarding a particular clinical procedure or treatment course must be made by the individual clinician, in light of the patient's clinical presentation, patient preferences, and the available diagnostic and treatment options. As noted previously, the guideline can assist care providers, but the use of a CPG must always be considered as a recommendation, within the context of a provider's clinical judgment and patient values and preferences, in the care for an individual patient.

III. Recommendations

The following recommendations were made using a systematic approach considering four domains as per the Grading of Recommendations Assessment, Development and Evaluation (GRADE) approach as detailed in the section on Methods and Appendix E. These domains include: confidence in the quality of the evidence, balance of desirable and undesirable outcomes (i.e., benefits and harms), patient or provider values and preferences, and other implications, as appropriate (e.g., resource use, equity, acceptability).

Given the relevance of all four domains in grading recommendations, the Work Group encountered multiple instances in which confidence in the quality of the evidence was low or very low, while there was marked imbalance of benefits and harms, as well as certain other important considerations arising from the domains of values and preferences and/or other implications. In particular, the harms due to the potential for severe adverse events associated with opioids, particularly overdose and OUD, often far outweigh the potential benefits. As such, in accounting for all four domains, these factors contributed to Strong recommendations in multiple instances.

#	Recommendation	Strength*	Category†
Initiation and Continuation of Opioids			
1.	a) We recommend against initiation of long-term opioid therapy for chronic pain. b) We recommend alternatives to opioid therapy such as self-management strategies and other non-pharmacological treatments. c) When pharmacologic therapies are used, we recommend non-opioids over opioids.	a) Strong against b) Strong for c) Strong for	Reviewed, New-replaced
2.	If prescribing opioid therapy for patients with chronic pain, we recommend a short duration. Note: Consideration of opioid therapy beyond 90 days requires re-evaluation and discussion with patient of risks and benefits.	Strong for	Reviewed, New-added
3.	For patients currently on long-term opioid therapy, we recommend ongoing risk mitigation strategies (see Recommendations 7-9), assessment for opioid use disorder, and consideration for tapering when risks exceed benefits (see Recommendation 14).	Strong for	Reviewed, New-replaced
4.	a) We recommend against long-term opioid therapy for pain in patients with untreated substance use disorder. b) For patients currently on long-term opioid therapy with evidence of untreated substance use disorder, we recommend close monitoring, including engagement in substance use disorder treatment, and discontinuation of opioid therapy for pain with appropriate tapering (see Recommendation 14 and Recommendation 17).	a) Strong against b) Strong for	Reviewed, Amended
5.	We recommend against the concurrent use of benzodiazepines and opioids. Note: For patients currently on long-term opioid therapy and benzodiazepines, consider tapering one or both when risks exceed benefits and obtaining specialty consultation as appropriate (see Recommendation 14 and the VA/DoD Clinical Practice Guideline for the Management of Substance Use Disorders).	Strong against	Reviewed, New-added

#	Recommendation	Strength*	Category†
6.	a) We recommend against long-term opioid therapy for patients less than 30 years of age secondary to higher risk of opioid use disorder and overdose. b) For patients less than 30 years of age currently on long-term opioid therapy, we recommend close monitoring and consideration for tapering when risks exceed benefits (see Recommendation 14 and Recommendation 17).	a) Strong against b) Strong for	Reviewed, New-replaced
Risk Mitigation			
7.	We recommend implementing risk mitigation strategies upon initiation of long-term opioid therapy, starting with an informed consent conversation covering the risks and benefits of opioid therapy as well as alternative therapies. The strategies and their frequency should be commensurate with risk factors and include: ■ Ongoing, random urine drug testing (including appropriate confirmatory testing) ■ Checking state prescription drug monitoring programs ■ Monitoring for overdose potential and suicidality ■ Providing overdose education ■ Prescribing of naloxone rescue and accompanying education	Strong for	Reviewed, New-replaced
8.	We recommend assessing suicide risk when considering initiating or continuing long-term opioid therapy and intervening when necessary.	Strong for	Reviewed, Amended
9.	We recommend evaluating benefits of continued opioid therapy and risk for opioid-related adverse events at least every three months.	Strong for	Reviewed, New-replaced
Type, Dose, Follow-up, and Taper of Opioids			
10.	If prescribing opioids, we recommend prescribing the lowest dose of opioids as indicated by patient-specific risks and benefits. Note: There is no absolutely safe dose of opioids.	Strong for	Reviewed, New-replaced
11.	As opioid dosage and risk increase, we recommend more frequent monitoring for adverse events including opioid use disorder and overdose. Note: ■ Risks for opioid use disorder start at any dose and increase in a dose dependent manner. ■ Risks for overdose and death significantly increase at a range of 20-50 mg morphine equivalent daily dose.	Strong for	Reviewed, New-replaced
12.	We recommend against opioid doses over 90 mg morphine equivalent daily dose for treating chronic pain. Note: For patients who are currently prescribed doses over 90 mg morphine equivalent daily dose, evaluate for tapering to reduced dose or to discontinuation (see Recommendations 14 and 15).	Strong against	Reviewed, New-replaced
13.	We recommend against prescribing long-acting opioids for acute pain, as an as-needed medication, or on initiation of long-term opioid therapy.	Strong against	Reviewed, New-replaced
14.	We recommend tapering to reduced dose or to discontinuation of long-term opioid therapy when risks of long-term opioid therapy outweigh benefits. Note: Abrupt discontinuation should be avoided unless required for immediate safety concerns.	Strong for	Reviewed, New-added

#	Recommendation	Strength*	Category†
15.	We recommend individualizing opioid tapering based on risk assessment and patient needs and characteristics. Note: There is insufficient evidence to recommend for or against specific tapering strategies and schedules.	Strong for	Reviewed, New-added
16.	We recommend interdisciplinary care that addresses pain, substance use disorders, and/or mental health problems for patients presenting with high risk and/or aberrant behavior.	Strong for	Reviewed, New-replaced
17.	We recommend offering medication assisted treatment for opioid use disorder to patients with chronic pain and opioid use disorder. Note: See the VA/DoD Clinical Practice Guideline for the Management of Substance Use Disorders.	Strong for	Reviewed, New-replaced
Opioid Therapy for Acute Pain			
18.	a) We recommend alternatives to opioids for mild-to-moderate acute pain. b) We suggest use of multimodal pain care including non-opioid medications as indicated when opioids are used for acute pain. c) If take-home opioids are prescribed, we recommend that immediate-release opioids are used at the lowest effective dose with opioid therapy reassessment no later than 3-5 days to determine if adjustments or continuing opioid therapy is indicated. Note: Patient education about opioid risks and alternatives to opioid therapy should be offered.	a) Strong for b) Weak for c) Strong for	Reviewed, New-added

*For additional information, please refer to the section on Grading Recommendations.

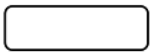
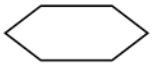
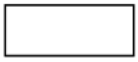
†For additional information, please refer to the section on Recommendation Categorization and Appendix H.

IV. Algorithm

This CPG follows an algorithm that is designed to facilitate understanding of the clinical pathway and decision making process used in management of LOT. The use of the algorithm format as a way to represent patient management was chosen based on the understanding that such a format may promote more efficient diagnostic and therapeutic decision making and has the potential to change patterns of resource use. Although the Work Group recognizes that not all clinical practices are linear, the simplified linear approach depicted through the algorithm and its format allows the provider to assess the critical information needed at the major decision points in the clinical process. It includes:

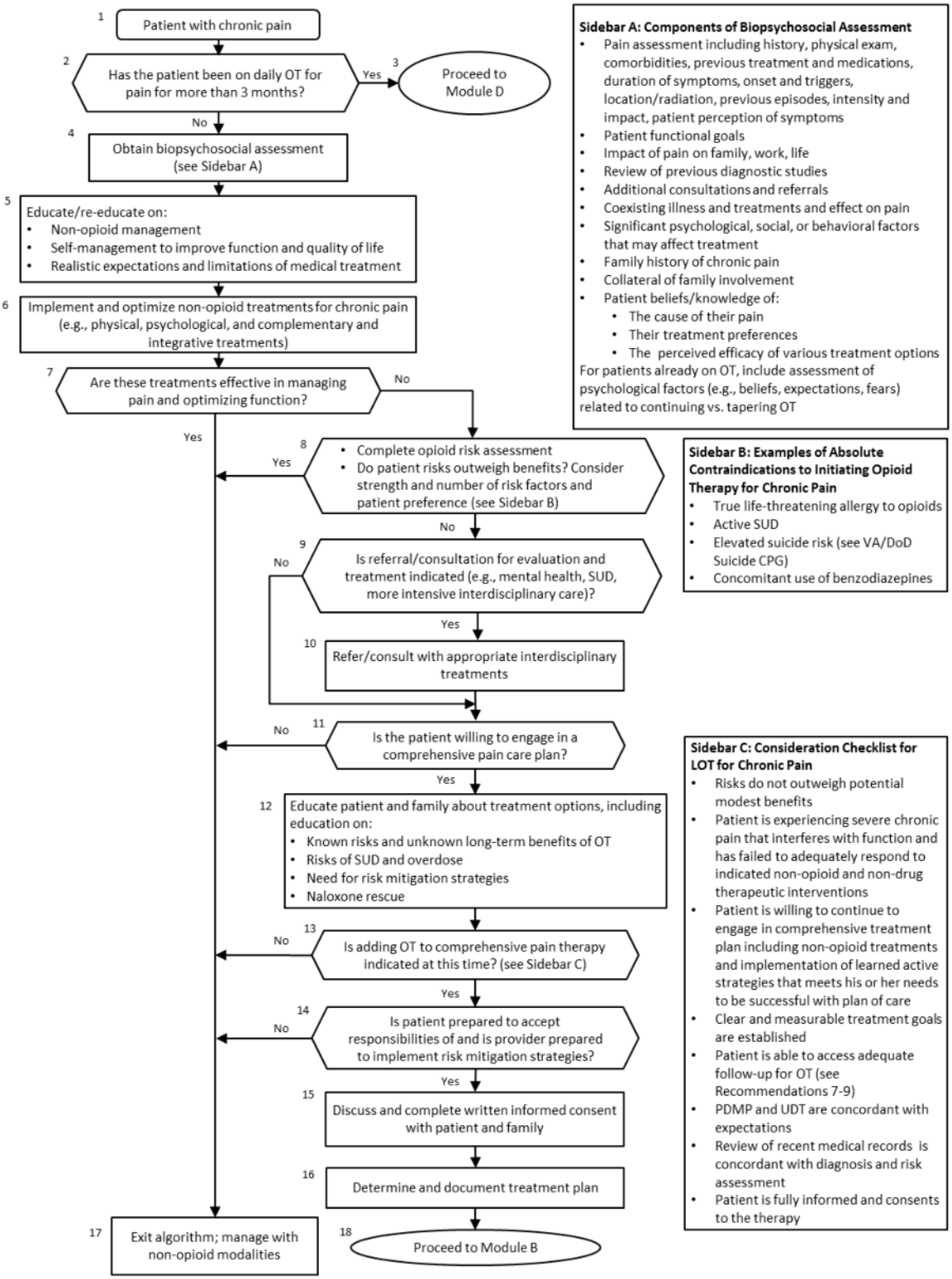
- An ordered sequence of steps of care
- Recommended observations and examinations
- Decisions to be considered
- Actions to be taken

For each guideline, the corresponding clinical algorithm is depicted by a step-by-step decision tree. Standardized symbols are used to display each step in the algorithm, and arrows connect the numbered boxes indicating the order in which the steps should be followed.[2]

	Rounded rectangles represent a clinical state or condition.
	Hexagons represent a decision point in the guideline, formulated as a question that can be answered Yes or No.
	Rectangles represent an action in the process of care.

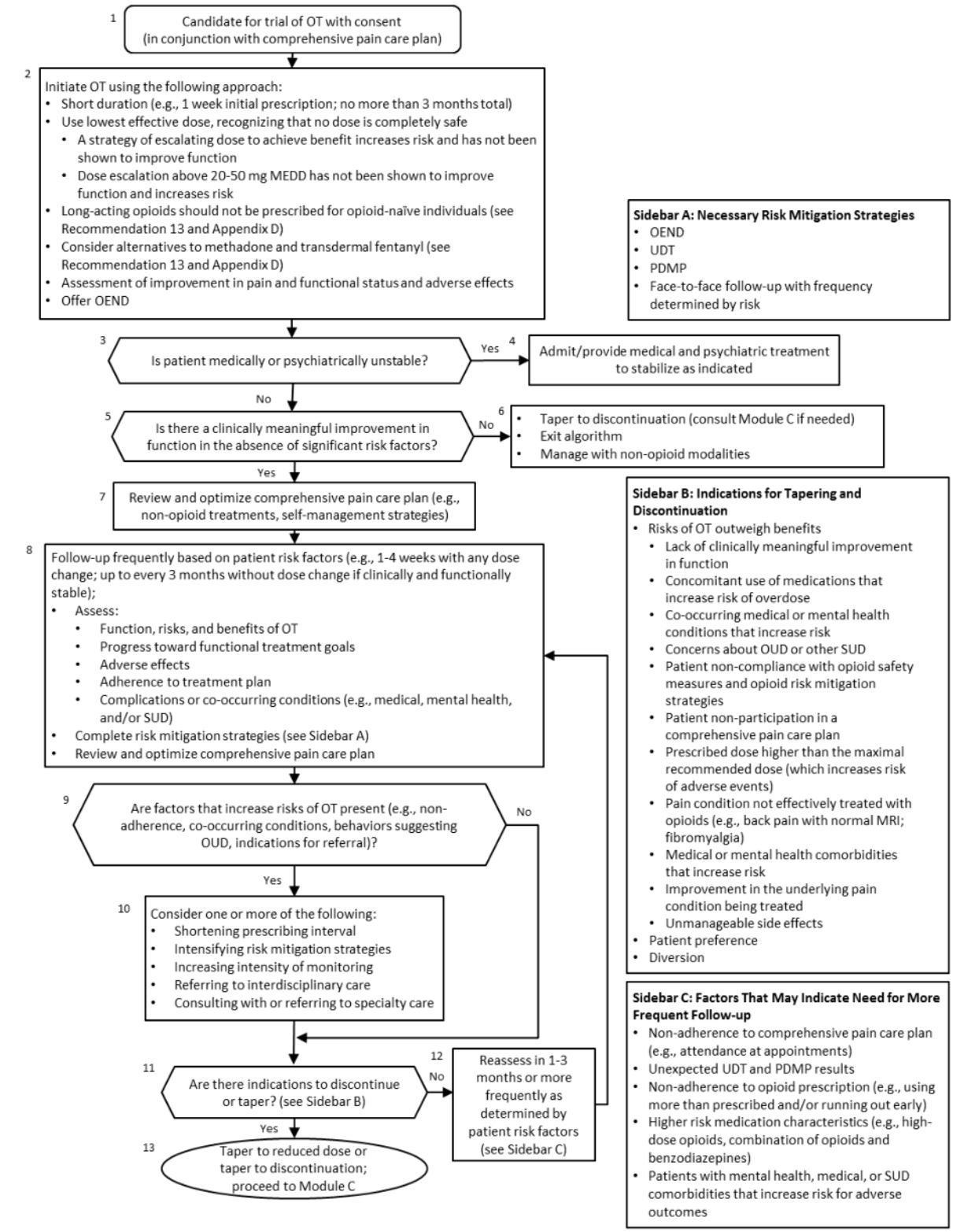
A. Module A: Determination of Appropriateness for Opioid Therapy

Note: Non-pharmacologic and non-opioid pharmacologic therapies are preferred for chronic pain.


1 Patient with chronic pain
2 Has the patient been on daily OT for pain for more than 3 months?
Yes
3 Proceed to Module D
No
4 Obtain biopsychosocial assessment (see Sidebar A)
5 Educate/re-educate on:
• Non-opioid management
• Self-management to improve function and quality of life
• Realistic expectations and limitations of medical treatment
6 Implement and optimize non-opioid treatments for chronic pain (e.g., physical, psychological, and complementary and integrative treatments)
7 Are these treatments effective in managing pain and optimizing function?
No
Yes
8 • Complete opioid risk assessment
• Do patient risks outweigh benefits? Consider strength and number of risk factors and patient preference (see Sidebar B)
Yes
No
9 Is referral/consultation for evaluation and treatment indicated (e.g., mental health, SUD, more intensive interdisciplinary care)?
No
Yes
10 Refer/consult with appropriate interdisciplinary treatments
11 Is the patient willing to engage in a comprehensive pain care plan?
No
Yes
12 Educate patient and family about treatment options, including education on:
• Known risks and unknown long-term benefits of OT
• Risks of SUD and overdose
• Need for risk mitigation strategies
• Naloxone rescue
13 Is adding OT to comprehensive pain therapy indicated at this time? (see Sidebar C)
No
Yes
14 Is patient prepared to accept responsibilities of and is provider prepared to implement risk mitigation strategies?
No
Yes
15 Discuss and complete written informed consent with patient and family
16 Determine and document treatment plan
17 Exit algorithm; manage with non-opioid modalities
18 Proceed to Module B
Sidebar A: Components of Biopsychosocial Assessment
• Pain assessment including history, physical exam, comorbidities, previous treatment and medications, duration of symptoms, onset and triggers, location/radiation, previous episodes, intensity and impact, patient perception of symptoms
• Patient functional goals
• Impact of pain on family, work, life
• Review of previous diagnostic studies
• Additional consultations and referrals
• Coexisting illness and treatments and effect on pain
• Significant psychological, social, or behavioral factors that may affect treatment
• Family history of chronic pain
• Collateral of family involvement
• Patient beliefs/knowledge of:
• The cause of their pain
• Their treatment preferences
• The perceived efficacy of various treatment options
For patients already on OT, include assessment of psychological factors (e.g., beliefs, expectations, fears) related to continuing vs. tapering OT
Sidebar B: Examples of Absolute Contraindications to Initiating Opioid Therapy for Chronic Pain
• True life-threatening allergy to opioids
• Active SUD
• Elevated suicide risk (see VA/DoD Suicide CPG)
• Concomitant use of benzodiazepines
Sidebar C: Consideration Checklist for LOT for Chronic Pain
• Risks do not outweigh potential modest benefits
• Patient is experiencing severe chronic pain that interferes with function and has failed to adequately respond to indicated non-opioid and non-drug therapeutic interventions
• Patient is willing to continue to engage in comprehensive treatment plan including non-opioid treatments and implementation of learned active strategies that meets his or her needs to be successful with plan of care
• Clear and measurable treatment goals are established
• Patient is able to access adequate follow-up for OT (see Recommendations 7-9)
• PDMP and UDT are concordant with expectations
• Review of recent medical records is concordant with diagnosis and risk assessment
• Patient is fully informed and consents to the therapy

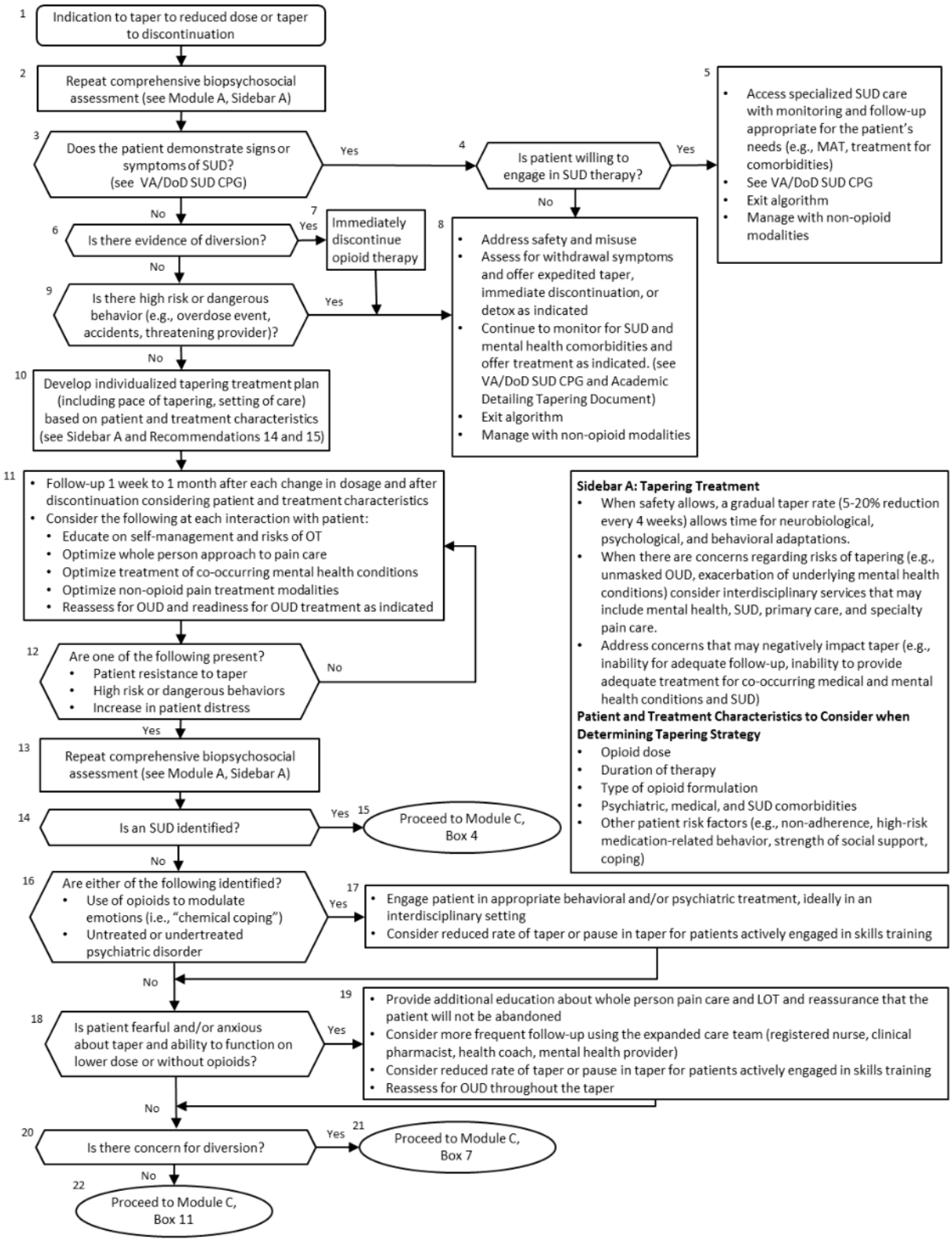
Abbreviations: LOT: long-term opioid therapy; OT: opioid therapy; PDMP: Prescription Drug Monitoring Program; SUD: substance use disorders; UDT: urine drug test; VA/DoD Suicide CPG: VA/DoD Clinical Practice Guideline for the Assessment and Management of Patients at Risk for Suicide

B. Module B: Treatment with Opioid Therapy


1
Candidate for trial of OT with consent (in conjunction with comprehensive pain care plan)
2
Initiate OT using the following approach:
• Short duration (e.g., 1 week initial prescription; no more than 3 months total)
• Use lowest effective dose, recognizing that no dose is completely safe
• A strategy of escalating dose to achieve benefit increases risk and has not been shown to improve function
• Dose escalation above 20-50 mg MEDD has not been shown to improve function and increases risk
• Long-acting opioids should not be prescribed for opioid-naïve individuals (see Recommendation 13 and Appendix D)
• Consider alternatives to methadone and transdermal fentanyl (see Recommendation 13 and Appendix D)
• Assessment of improvement in pain and functional status and adverse effects
• Offer OEND
Sidebar A: Necessary Risk Mitigation Strategies
• OEND
• UDT
• PDMP
• Face-to-face follow-up with frequency determined by risk
3
Is patient medically or psychiatrically unstable?
Yes
4
Admit/provide medical and psychiatric treatment to stabilize as indicated
No
5
Is there a clinically meaningful improvement in function in the absence of significant risk factors?
No
6
• Taper to discontinuation (consult Module C if needed)
• Exit algorithm
• Manage with non-opioid modalities
Yes
7
Review and optimize comprehensive pain care plan (e.g., non-opioid treatments, self-management strategies)
8
Follow-up frequently based on patient risk factors (e.g., 1-4 weeks with any dose change; up to every 3 months without dose change if clinically and functionally stable);
• Assess:
• Function, risks, and benefits of OT
• Progress toward functional treatment goals
• Adverse effects
• Adherence to treatment plan
• Complications or co-occurring conditions (e.g., medical, mental health, and/or SUD)
• Complete risk mitigation strategies (see Sidebar A)
• Review and optimize comprehensive pain care plan
Sidebar B: Indications for Tapering and Discontinuation
• Risks of OT outweigh benefits
• Lack of clinically meaningful improvement in function
• Concomitant use of medications that increase risk of overdose
• Co-occurring medical or mental health conditions that increase risk
• Concerns about OUD or other SUD
• Patient non-compliance with opioid safety measures and opioid risk mitigation strategies
• Patient non-participation in a comprehensive pain care plan
• Prescribed dose higher than the maximal recommended dose (which increases risk of adverse events)
• Pain condition not effectively treated with opioids (e.g., back pain with normal MRI; fibromyalgia)
• Medical or mental health comorbidities that increase risk
• Improvement in the underlying pain condition being treated
• Unmanageable side effects
• Patient preference
• Diversion
9
Are factors that increase risks of OT present (e.g., non-adherence, co-occurring conditions, behaviors suggesting OUD, indications for referral)?
No
Yes
10
Consider one or more of the following:
• Shortening prescribing interval
• Intensifying risk mitigation strategies
• Increasing intensity of monitoring
• Referring to interdisciplinary care
• Consulting with or referring to specialty care
Sidebar C: Factors That May Indicate Need for More Frequent Follow-up
• Non-adherence to comprehensive pain care plan (e.g., attendance at appointments)
• Unexpected UDT and PDMP results
• Non-adherence to opioid prescription (e.g., using more than prescribed and/or running out early)
• Higher risk medication characteristics (e.g., high-dose opioids, combination of opioids and benzodiazepines)
• Patients with mental health, medical, or SUD comorbidities that increase risk for adverse outcomes
11
Are there indications to discontinue or taper? (see Sidebar B)
No
12
Reassess in 1-3 months or more frequently as determined by patient risk factors (see Sidebar C)
Yes
13
Taper to reduced dose or taper to discontinuation; proceed to Module C

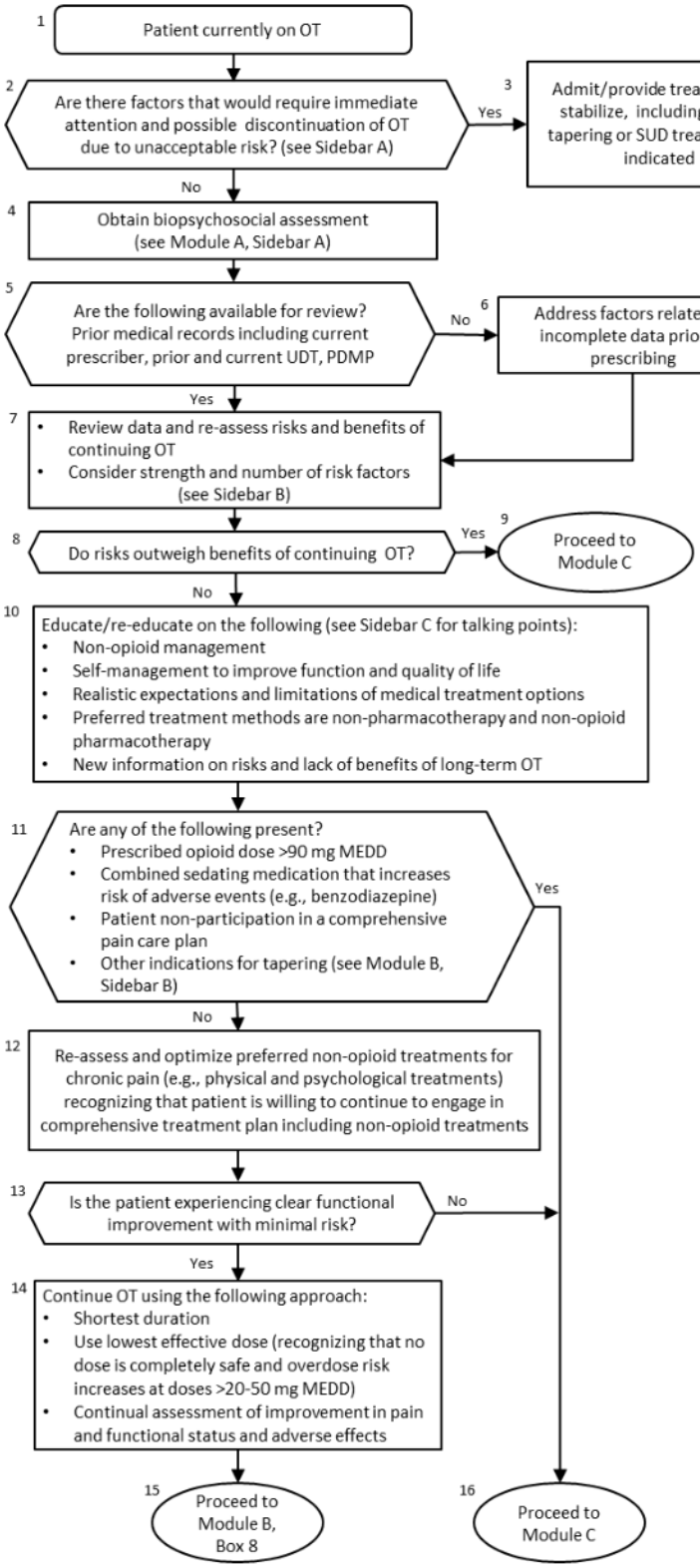
Abbreviations: MEDD: morphine equivalent daily dose; mg: milligram(s); MRI: magnetic resonance imaging; OEND: Overdose Education and Naloxone Distribution; OT: opioid therapy; OUD: opioid use disorder; PDMP: Prescription Drug Monitoring Program; SUD: substance use disorders; UDT: urine drug test

C. Module C: Tapering or Discontinuation of Opioid Therapy


1
Indication to taper to reduced dose or taper to discontinuation
2
Repeat comprehensive biopsychosocial assessment (see Module A, Sidebar A)
3
Does the patient demonstrate signs or symptoms of SUD? (see VA/DoD SUD CPG)
Yes
4
Is patient willing to engage in SUD therapy?
Yes
5
• Access specialized SUD care with monitoring and follow-up appropriate for the patient's needs (e.g., MAT, treatment for comorbidities)
• See VA/DoD SUD CPG
• Exit algorithm
• Manage with non-opioid modalities
No
6
Is there evidence of diversion?
Yes
7
Immediately discontinue opioid therapy
No
8
• Address safety and misuse
• Assess for withdrawal symptoms and offer expedited taper, immediate discontinuation, or detox as indicated
• Continue to monitor for SUD and mental health comorbidities and offer treatment as indicated. (see VA/DoD SUD CPG and Academic Detailing Tapering Document)
• Exit algorithm
• Manage with non-opioid modalities
9
Is there high risk or dangerous behavior (e.g., overdose event, accidents, threatening provider)?
Yes
No
10
Develop individualized tapering treatment plan (including pace of tapering, setting of care) based on patient and treatment characteristics (see Sidebar A and Recommendations 14 and 15)
11
• Follow-up 1 week to 1 month after each change in dosage and after discontinuation considering patient and treatment characteristics
• Consider the following at each interaction with patient:
• Educate on self-management and risks of OT
• Optimize whole person approach to pain care
• Optimize treatment of co-occurring mental health conditions
• Optimize non-opioid pain treatment modalities
• Reassess for OUD and readiness for OUD treatment as indicated
12
Are one of the following present?
• Patient resistance to taper
• High risk or dangerous behaviors
• Increase in patient distress
No
Yes
13
Repeat comprehensive biopsychosocial assessment (see Module A, Sidebar A)
14
Is an SUD identified?
Yes
15
Proceed to Module C, Box 4
No
16
Are either of the following identified?
• Use of opioids to modulate emotions (i.e., "chemical coping")
• Untreated or undertreated psychiatric disorder
Yes
17
• Engage patient in appropriate behavioral and/or psychiatric treatment, ideally in an interdisciplinary setting
• Consider reduced rate of taper or pause in taper for patients actively engaged in skills training
No
18
Is patient fearful and/or anxious about taper and ability to function on lower dose or without opioids?
Yes
19
• Provide additional education about whole person pain care and LOT and reassurance that the patient will not be abandoned
• Consider more frequent follow-up using the expanded care team (registered nurse, clinical pharmacist, health coach, mental health provider)
• Consider reduced rate of taper or pause in taper for patients actively engaged in skills training
• Reassess for OUD throughout the taper
No
20
Is there concern for diversion?
Yes
21
Proceed to Module C, Box 7
No
22
Proceed to Module C, Box 11
Sidebar A: Tapering Treatment
• When safety allows, a gradual taper rate (5-20% reduction every 4 weeks) allows time for neurobiological, psychological, and behavioral adaptations.
• When there are concerns regarding risks of tapering (e.g., unmasked OUD, exacerbation of underlying mental health conditions) consider interdisciplinary services that may include mental health, SUD, primary care, and specialty pain care.
• Address concerns that may negatively impact taper (e.g., inability for adequate follow-up, inability to provide adequate treatment for co-occurring medical and mental health conditions and SUD)
Patient and Treatment Characteristics to Consider when Determining Tapering Strategy
• Opioid dose
• Duration of therapy
• Type of opioid formulation
• Psychiatric, medical, and SUD comorbidities
• Other patient risk factors (e.g., non-adherence, high-risk medication-related behavior, strength of social support, coping)

Abbreviations: LOT: long-term opioid therapy; MAT: medication assisted treatment; OT: opioid therapy; OUD: opioid use disorder; SUD: substance use disorders; VA/DoD SUD CPG: VA/DoD Clinical Practice Guideline for the Management of Substance Use Disorders

D. Module D: Patients Currently on Opioid Therapy


1
Patient currently on OT
2
Are there factors that would require immediate attention and possible discontinuation of OT due to unacceptable risk? (see Sidebar A)
Yes
3
Admit/provide treatment to stabilize, including opioid tapering or SUD treatment as indicated
No
4
Obtain biopsychosocial assessment (see Module A, Sidebar A)
5
Are the following available for review? Prior medical records including current prescriber, prior and current UDT, PDMP
No
6
Address factors related to incomplete data prior to prescribing
Yes
7
Review data and re-assess risks and benefits of continuing OT
Consider strength and number of risk factors (see Sidebar B)
8
Do risks outweigh benefits of continuing OT?
Yes
9
Proceed to Module C
No
10
Educate/re-educate on the following (see Sidebar C for talking points):
Non-opioid management
Self-management to improve function and quality of life
Realistic expectations and limitations of medical treatment options
Preferred treatment methods are non-pharmacotherapy and non-opioid pharmacotherapy
New information on risks and lack of benefits of long-term OT
11
Are any of the following present?
Prescribed opioid dose >90 mg MEDD
Combined sedating medication that increases risk of adverse events (e.g., benzodiazepine)
Patient non-participation in a comprehensive pain care plan
Other indications for tapering (see Module B, Sidebar B)
Yes
No
12
Re-assess and optimize preferred non-opioid treatments for chronic pain (e.g., physical and psychological treatments) recognizing that patient is willing to continue to engage in comprehensive treatment plan including non-opioid treatments
13
Is the patient experiencing clear functional improvement with minimal risk?
No
Yes
14
Continue OT using the following approach:
Shortest duration
Use lowest effective dose (recognizing that no dose is completely safe and overdose risk increases at doses >20-50 mg MEDD)
Continual assessment of improvement in pain and functional status and adverse effects
15
Proceed to Module B, Box 8
16
Proceed to Module C

Sidebar A: Factors Requiring Immediate Attention and Possible Discontinuation

- Untreated SUD
- Unstable mental health disorder
- Medical condition that acutely increases opioid risks (e.g., compromised or worsening cognitive or cardiopulmonary status)
- Other factors that acutely increase risk of overdose
  - Recent overdose
  - Current sedation
  - Recent motor vehicle accident
- Acutely elevated suicide risk (see VA/DoD Suicide CPG)

Sidebar B: Considerations During Re-assessment

Risks

- Increase in all-cause mortality
- Increase risk of unintentional overdose death
- Increase risk of developing OUD
- Risk of developing or worsening:
  - Depression
  - Falls
  - Fractures
  - Sleep disordered breathing
  - Worsening pain
  - Motor vehicle accidents
  - Hypogonadism
  - Prolonged pain
  - Nausea
  - Constipation
  - Dry mouth
  - Sedation
  - Cognitive dysfunction
  - Immune system dysfunction
  - Reduction in function
  - Reduction in quality of life

Benefits

- Modest short-term improvement in pain
- Possible short-term improvement in function

Sidebar C: Talking Points for Education and Re-education for Patients Currently on OT

- "Doctors used to think that opioids were safe and effective when used for long periods of time to treat chronic pain."
- "New information has taught us that long-term opioid use can lead to multiple problems including loss of pain relieving effects, increased pain, unintentional death, OUD, and problems with sleep, mood, hormonal dysfunction, and immune dysfunction."
- "We now know that the best treatments for chronic pain are not opioids. The best treatments for chronic pain are non-drug treatments such as psychological therapies and rehabilitation therapies and non-opioid medications."

Abbreviations: MEDD: morphine equivalent daily dose; mg: milligram(s); OT: opioid therapy; OUD: opioid use disorder; PDMP: Prescription Drug Monitoring Program; SUD: substance use disorders; UDT: urine drug test; VA/DoD Suicide CPG: VA/DoD Clinical Practice Guideline for the Assessment and Management of Patients at Risk for Suicide

V. Background

A. Opioid Epidemic

Chronic pain is a national public health problem as outlined in the 2011 study by the National Academy of Medicine (previously the Institute of Medicine [IOM]).[3] At least 100 million Americans suffer from some form of chronic pain. Until recently, the treatment of chronic pain with opioids was increasing at an alarming rate. The increase in prescriptions of these medications has been accompanied by an epidemic of opioid-related adverse events.

From 2000 through 2010, the proportion of pain visits during which opioid and non-opioid pharmacologic therapies were prescribed increased from 11.3% to 19.6% and from 26% to 29%, respectively.[4] In 2012, for every 100 persons in the United States (U.S.), 82.5 opioid prescriptions and 37.6 benzodiazepine prescriptions were written by healthcare providers.[5] In the emergency department, at least 17% of discharges included prescriptions for opioids.[6,7]

There has been limited research on the effectiveness of LOT for non-end-of-life pain. At the same time, there is mounting evidence of the ill effects of LOT, including increased mortality, OUD, overdose, sexual dysfunction, fractures, myocardial infarction, constipation, and sleep-disordered breathing.[8-10] Despite increasing awareness of the known harms of opioids, 259 million opioid prescriptions were still written in 2012.[11]

The increase in opioid prescribing is matched by a parallel increase in morbidity, mortality, opioid-related overdose death rates, and substance use disorders (SUD) treatment admissions from 1999 to 2008.[12,13] In 2009, drug overdose became the leading cause of injury-related death in the U.S., surpassing deaths from traffic accidents.[14] In 2014, 1.9 million Americans were affected by an OUD related to non-medical use of prescription pain relievers,[15] and in the same year, 18,893 individuals died as a result of a prescription drug overdose.[16] There has been a four-fold increase in the absolute number of deaths associated with use of opioids since 2000, and a 14% increase between 2013 and 2014 alone.[17] In a survey of patients prescribed opioids for chronic non-cancer pain (CNCP) and their family members, 34% of patients reported that they thought they were “addicted” or “dependent” on opioid pain medication, 34% said that they used the medication for “fun” or to “get high,” while 22% used the medication to relieve day-to-day stress.[18]

Concurrent with the increase in prescription opioid use, the rate of heroin overdose deaths increased nearly four-fold between 2000 and 2013.[19] According to a survey of patients entering SUD treatment for heroin use, the prescription opioid epidemic has resulted in a marked shift in how and which opioids are abused. In the 1960s, 80% of people entering treatment for heroin use started using heroin as their first opioid, while in the 2000s, 75% of people entering treatment for heroin use started using prescription opioids as their first opioid.[20] This increase in the use of opioids, as well as associated morbidity,

mortality, and other adverse outcomes, has called attention to the need for a paradigm shift in pain and in the way it is treated. Consult the VA/DoD Clinical Practice Guideline for the Management of Substance Use Disorders (VA/DoD SUD CPG)[1] for further information.

B. Paradigm Shift in Pain and Its Treatment

The U.S. is in the midst of a cultural transformation in the way pain is viewed and treated. The biomedical model of pain care, in which the pain experience is reduced to a pain generator and pain treatment is aimed at fixing or numbing pain with medications, interventions, or surgery, dominated the 1990s and the first decade of the 2000s. As the cost, potential harm, and limited effectiveness of this approach to chronic pain was becoming apparent, the National Academy of Medicine issued a call for the transformation of pain care to a biopsychosocial, multimodal, interdisciplinary model.[3]

A paradigm shift in the use of OT for chronic non-terminal pain has paralleled this transformation in pain care. Prior to the 1980s, OT was rarely used outside of severe acute injury or post-surgical pain, primarily due to concern for tolerance, physical dependence, and addiction. As the hospice and palliative care movement began defining end-of-life care in the U.S. during the 1980s and emphasizing the importance of pain relief, OT increasingly became a mainstay for cancer and end-of-life pain. Efforts to destigmatize the use of prescription opioids for chronic non-terminal pain encompassed primary care providers and the public. The efforts led to an unprecedented increase in opioid prescribing for chronic non-terminal pain. Chronic pain management became synonymous with LOT in the 1990s and the first decade of the 2000s with significant numbers of patients in pain clinics receiving LOT.[21] Despite the absence of long-term safety or efficacy data, OT for chronic non-terminal pain became a mainstay of therapy. However, as observational and epidemiologic data of harm from LOT accumulated, a much more cautious approach to OT for chronic non-terminal pain has emerged in the decade of the 2010s.

The accumulation of evidence of harms and the absence of evidence of long-term benefits has warranted a newly cautious approach to LOT that prioritizes safety. This approach coupled with the evidence of both the safety and efficacy for non-pharmacologic and non-opioid pharmacologic pain therapies has led to the current transformation in the way in which pain is viewed and treated. The biopsychosocial model of pain recognizes pain as a complex multidimensional experience that requires multimodal and integrated care approaches. Within this context, non-pharmacologic treatments and non-opioid medications are the preferred treatments for chronic non-terminal pain. OT has a limited role, primarily in the treatment of severe acute pain, post-operative pain, and end-of-life pain.

C. Prioritizing Safe Opioid Prescribing Practices and Use

The increasing use of opioids, as well as the accompanying rise in morbidity and mortality associated with opioid use, has garnered increasing attention from federal and local officials as well as other policy makers.

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[1] See the VA/DoD Clinical Practice Guideline for the Management of Substance Use Disorders. Available at: http://www.healthquality.va.gov/guidelines/mh/sud/index.asp.

This public health issue, which has been labelled an epidemic,[22] became a focus of the President's National Drug Control Strategy in 2010 and has since remained a focus. Two main goals introduced in the 2010 strategy included curtailing illicit drug consumption in America and improving the health and safety of the American people by reducing the consequences of drug abuse.[23] The 2015 strategy, and an accompanying presidential memorandum on preventing prescription drug abuse and heroin use, released in October 2015, encouraged the improvement of health and safety using evidence-based methods by calling for change in a number of key areas including preventing drug use in communities, seeking early intervention opportunities, and integrating SUD treatment and supporting recovery.[24,25]

With the passage of the Patient Protection and Affordable Care Act (PPACA) in March 2010, the Interagency Pain Research Coordinating Committee was created to coordinate pain research efforts throughout federal government agencies. The Committee was tasked with summarizing advances in pain care research, identifying gaps in research, and developing recommendations regarding ways to minimize duplicative efforts, disseminate pain care information, and expand public/private research partnerships and collaborations. The Committee published the National Pain Strategy in March 2016 in response to the call from the National Academy of Medicine to increase awareness of pain as a significant public health issue in the U.S.[3] The strategy made recommendations in a number of areas including prevention and care, professional education and training, and population research. The plan is aimed at decreasing the prevalence of all types of pain (acute and chronic) in the U.S., as well as the disability and morbidity associated with pain.[26]

Government agencies, including the VA, DoD, and Substance Abuse and Mental Health Services Administration (SAMHSA), have also launched initiatives to improve the study and treatment of pain and adverse events associated with opioid analgesics such as OUD and overdose.[27] By August 2013, the VA deployed the Opioid Safety Initiative (OSI) requirements to all Veterans Integrated Service Networks (VISNs) with the aim of ensuring opioids are used in a safe, effective, and judicious manner. The goals of the OSI related to such topics as increased education, monitoring, use of safe and effective prescribing and management methods, tool development, collaboration, and use of alternative pain treatment. The OSI uses the Veterans Health Administration (VHA's) electronic health record to identify patients who may be high-risk for adverse outcomes with use of opioids and providers whose prescribing practices do not reflect best evidence so that patient care can be improved. The OSI requirements include specific indicators (e.g., the number of unique pharmacy patients dispensed an opioid, the unique patients on LOT who have received UDT).[28] As part of the OSI, the VA launched the Opioid Overdose Education and Naloxone Distribution (OEND) program, which was implemented as a risk mitigation strategy aimed at reducing deaths from opioid overdose. The program components included education and training regarding the following topics: opioid overdose prevention, recognition, and rescue response; risk mitigation strategies; and issuing naloxone kits, which can be used as an antidote to opioid overdose.[29,30]

Other initiatives are aimed at improving the safe use of opioids, including the OSI Toolkit and the patient guide *Taking Opioids Responsibly for Your Safety and the Safety of Others: Patient Information Guide on Long-term Opioid Therapy for Chronic Pain*. The OSI Toolkit was developed to provide clinicians with materials to inform clinical decision-making regarding opioid therapy and safe opioid prescribing.[31] The toolkit materials can be found at the following link:

https://www.va.gov/PAINMANAGEMENT/Opioid_Safety_Initiative_Toolkit.asp. *Taking Opioids Responsibly for Your Safety and the Safety of Others: Patient Information Guide on Long-term Opioid Therapy for Chronic Pain* is aimed at providing information to patients as well as their providers regarding the safe use of opioids. More information can be found at the following link: http://www.healthquality.va.gov/guidelines/Pain/cot/OpiodTheraphyforChronicPainPatientTool20May2013print.pdf. To further promote safety and patient centered care, the VHA issued a policy in 2014 requiring standardized education and signature informed consent for all patients receiving LOT for non-cancer pain.[32]

The aforementioned presidential memorandum of October 2015 mandated that executive departments and agencies shall, to the extent permitted by law, provide training on the appropriate and effective prescribing of opioid medications to all employees who are health care professionals and who prescribe controlled substances as part of their federal responsibilities and duties. The DoD Opioid Prescriber Safety Training Program, launched accordingly, includes modules on pain management and opioid prescribing safety, the recent Centers for Disease Control and Prevention (CDC) guideline (see the below paragraph), and the identification of substance misuse and referral to specialized services. Defense Centers of Excellence for Psychological Health and Traumatic Brain Injury is sponsoring the training and related management support. Training is available online at http://opstp.cds.pesgce.com/hub.php.

The CDC released its *Guideline for Prescribing Opioids for Chronic Pain*, directed toward primary care physicians, on March 15, 2016.[33] The aim of the guideline is to assist primary care providers in offering safe and effective treatment for patients with chronic pain in the outpatient setting (not including active cancer treatment, palliative care, or end-of-life care). It is also aimed at improving communication between providers and patients and decreasing adverse outcomes associated with LOT. The CDC guideline, similar to the VA/DoD OT CPG, covered topics including initiation and continuation of OT, management of OT, and risk assessment and use of risk mitigation strategies. It also used the GRADE system to assign a grade for the strength for each recommendation which includes assessment of the quality of the evidence and consideration of the balance of desirable and undesirable outcomes, patient values and preferences, and other considerations (e.g., resource use, equity) during recommendation development (see Grading Recommendations for more information on the use of GRADE in updating this CPG).

On July 22, 2016, the Comprehensive Addiction and Recovery Act (CARA) was enacted with the aim of addressing the epidemic of overdoses from prescription opioids and other prescription drugs and heroin.[34] While this act was primarily focused on opioid abuse treatment and prevention, it also gave specific instruction to the VA in regard to broad aspects of OT including consideration of the CDC guideline in revising the prior VA/DoD OT CPG and adopting it for the VA. There are, however, some important distinctions between the CDC guideline and the VA/DoD OT CPG.

The VA/DoD OT CPG was developed with a specific patient population in mind—Service Members, Veterans, and their families—that has unique characteristics and needs related to the military culture and communities to which they return. Throughout the VA/DoD OT CPG, attention is paid to the characteristics and needs of these patients, particularly regarding specific risk factors such as risk for suicide, SUD, and other medical and mental health co-occurring conditions that may complicate management of pain for these patients. Further, these recommendations were made keeping in mind the implications they would have within the VA/DoD healthcare settings, particularly regarding considerations such as resource use,

accessibility, and equity related to each recommendation. Finally, the recommendations were developed keeping in mind the urgent need for rigorous attention to the balance of risks and benefits for patients within the VA/DoD specifically.

There were also some differences in the methodology used between the development of the VA/DoD OT CPG and the CDC guideline. Along with a clinical evidence review, during which the evidence was evaluated using GRADE, the CDC guideline developers also considered the findings of a contextual evidence review. Further, the CDC Core Expert Group, which consisted of subject matter experts, representatives of primary care professional societies and state agencies, and an expert in guideline methodology, reviewed recommendations drafted by the CDC and evaluated how the evidence was used in the development of the recommendations, rather than developing the recommendations themselves (as was the VA/DoD OT Work Group's role in development of the VA/DoD OT CPG). While experts provided feedback on the CDC recommendations and their development, the CDC determined the final recommendations. CDC also used a review process considering and incorporating feedback from federal partners (e.g., SAMHSA, VA, DoD), stakeholders (e.g., professional organizations, delivery systems, community organizations), and other constituents (e.g., clinicians, prospective patients). The CDC guideline development process included notice in the *Federal Register* for a public review and comment period as well as peer review. Thus, the recommendations made in the CDC guideline, although similar to those made in this CPG, were likely based on a slightly different evidence base and revised based on the feedback of individuals who were considering a larger group of potential patients relative to the VA/DoD.

Thus, while the VA/DoD OT Work Group was aware of the release of the CDC guideline and considered potential implications, the CDC guideline did not form the basis of the deliberations on the strength or direction of these recommendations. The Work Group followed the VA/DoD Guideline for Guidelines, a document that details the process by which VA/DoD guidelines will be developed, including the use of the GRADE methodology.[1] As required by Congress in CARA, the Work Group reviewed and considered the CDC guideline and its inclusion in the VA/DoD OT CPG.[34]

D. Taxonomy

Pain is defined as "an unpleasant sensory and emotional experience associated with actual or potential tissue damage, or described in terms of such damage…Pain is always subjective…It is unquestionably a sensation in a part or parts of the body, but it is also always unpleasant and therefore also an emotional experience."[3,35] All of these facets signify the complexity of pain as a condition by itself and how it relates to both the brain and the body.[36] Pain as a symptom is multifaceted and is described and characterized by many factors such as its quality (e.g., sharp versus dull), intensity, timing, location, and whether it is associated with position or movement.

Chronic pain is defined as pain lasting three months or more.[37] It is often associated with changes in the central nervous system (CNS) known as central sensitization.[38] Whereas acute and subacute pain are thought to involve primarily nociceptive processing areas in the CNS, chronic pain is thought to be associated with alterations in brain centers involved with emotions, reward, and executive function as well as central sensitization of nociceptive pathways across several CNS areas.[39-41]

There are many causes of chronic pain. Pain arising from persistent peripheral stimulation could be mechanical or chemical/inflammatory in nature typically leading to well-localized nociceptive mechanism

pain. Mechanical or inflammatory pain with a visceral origin may produce a less localized pain. Neuropathic pain due to injury or disease of the central or peripheral nervous system (e.g., spinal cord injury, diabetic neuropathy, radiculopathy) may lead to poorly localized symptoms such as diffuse pain, burning, numbness, or a feeling of skin sensitivity.

A comprehensive pain assessment includes a biopsychosocial interview and focused physical exam. Elements of the biopsychosocial pain interview include a pain-related history, assessment of pertinent medical and psychiatric comorbidities including personal and family history of SUD, functional status and functional goals, coping strategies, and a variety of psychosocial factors such as the patient's beliefs and expectations about chronic pain and its treatment.[36] Patients with chronic pain may also experience worsened quality of life, mental health, immune system function, physical function, sleep, employment status, and impaired personal relationships.[3,42-44] Worsening of some of these factors (e.g., quality of life, change in employment status) seems to also be associated with pain severity and the presence of psychiatric comorbidities.[45,46] Patients with chronic pain report psychological complaints (e.g., depression, anxiety, poor self-efficacy, poor general emotional functioning) more often than patients without chronic pain.[47] Further, there can be social and psychological consequences such as decreased ability to successfully maintain relationship and career roles and increased depression, fear, and anxiety as a result of pain.[3,11]

E. Epidemiology and Impact

a. General Population

Chronic pain is among the most common, costly, and disabling chronic medical conditions in the U.S.[48-50] In the U.S., approximately 100 million adults experience chronic pain, and pain is associated with approximately 20% of ambulatory primary care and specialty visits.[3,4,11] As noted above (see Opioid Epidemic), since the late 1990s and early 2000s, the proportion of pain visits during which patients received opioids has increased significantly, as have opioid-related morbidity, mortality, overdose death, and SUD treatment admissions.[4,12,13] Approximately one in five patients with non-cancer pain or pain-related diagnoses is prescribed opioids in office-based settings.[4] According to the CDC, sales of prescription opioids U.S. quadrupled from 1999 and 2014.[12] The absolute number of deaths associated with use of opioids has increased four-fold since 2000, including by 14% from 2013 to 2014 alone.[17] Between 1999 and 2015, more than 183,000 people died from overdoses related to prescription opioids.[51] In one survey, approximately one-third of patients receiving OT for CNCP (or their family members) indicated thinking that they were "addicted" to or "dependent" on the medication or used the medication for "fun" or to "get high."[18] From 2000 through 2013, the rate of heroin overdose deaths increased nearly four-fold.[19] In the 2000s, the majority of people entering treatment for heroin use used prescription opioids as their first opioid.[20]

b. VA/DoD Population

From fiscal years 2004 to 2012, the prevalence of opioid prescriptions among Veterans increased from 18.9% to 33.4%, an increase of 76.7%. The groups with the highest prevalence of opioid use were women and young adults (i.e., 18-34 years old).[52] In a sample of non-treatment-seeking members of the military who were interviewed within three months of returning from Afghanistan, 44% reported chronic pain and 15% reported using opioids—percentages much higher than in the general population.[53,54] Chronic pain

was also associated with poorer physical function, independent of comorbid mental health concerns in Operation Enduring Freedom/Operation Iraqi Freedom (OEF/OIF) Veterans.[55]

In a study of Veterans with chronic pain who had been on opioids for at least 90 days, over 90% continued to use opioids one year later and nearly 80% continued to use opioids after completion of the 3.5 year follow-up period; while, in a study of civilian patients who had been on opioids for at least 90 days, approximately 65% remained on opioids through the 4.8 year follow-up period.[56,57] Rates of continuation in Veterans, based on this study, appeared to be related to age, marital status, race, geography, mental health comorbidity, and dosage. Compared to others, those who were age 50-65 years, were married, were a race other than African American, and who lived in a rural setting were more likely to continue using opioids. Veterans on higher doses of opioids were more likely to continue their use. Notably, those with mental health diagnoses were less likely to continue opioids, including those with schizophrenia and bipolar diagnoses.[56]

F. Chronic Pain and Co-occurring Conditions

Individuals with conditions that result in or co-occur with chronic pain may have different needs or respond to treatment differently than individuals with chronic pain alone. Many different physical and psychological conditions have a pain component that can be difficult to distinguish from the underlying mechanism of illness. Furthermore, the treatment of co-occurring pain and other conditions may vary or require special considerations during their management. Readers are encouraged to consult other VA/DoD CPGs for further information (see VA/DoD Clinical Practice Guidelines website: www.healthquality.va.gov).

G. Risk Factors for Adverse Outcomes of Opioid Therapy

The risk factors with the greatest impact for development of opioid-related adverse events are the duration and dose of opioid analgesic use. Beyond duration and dose of OT, many factors increase the risk of adverse outcomes and must be considered prior to initiating or continuing OT (Box 1).

Given the insufficient evidence of benefit for LOT, the clinician must carefully weigh harms and benefits and educate the patient as well as his or her family or caregiver prior to proceeding with treatment. As patient values and preferences may be impacted by other clinical considerations, some patients with one or more risk factors for adverse outcomes may differ with the clinician's assessment that the risks of OT outweigh the potential for modest short-term benefits. Thus, it is important to consider patients' values and concerns, address misconceptions, express empathy, and fully explain to patients with one or more risk factors that they may not benefit from, and may even be harmed by, treatment with OT.

Conditions that significantly increase the risk of adverse outcomes from LOT are listed below. Patients for whom LOT is initiated should be carefully monitored, and ongoing assessment of risk should be performed with vigilance for the development of additional risk factors and adverse outcomes (see Recommendations 7-9). Consider consultation with appropriate specialty care providers if there is uncertainty about whether benefits of OT, such as improved function (e.g., return-to-work), outweigh the risks.

Box 1: Selected Significant Risk Factors

- Duration and dose of OT
- Severe respiratory instability
- Sleep disordered breathing (e.g., sleep apnea)
- Acute psychiatric instability or intermediate to high acute suicide risk
  - Suicidality (see Recommendation 8; VA/DoD Clinical Practice Guideline for Assessment and Management of Patients at Risk for Suicide [VA/DoD Suicide CPG], available at: http://www.healthquality.va.gov/guidelines/MH/srb/)
- Mental disorders
  - Current or history of SUD (see VA/DoD SUD CPG, available at: http://www.healthquality.va.gov/guidelines/mh/sud/index.asp)
    - Untreated SUD confers additional risk (see Recommendation 4)
  - Depression or history of depression (see VA/DoD Clinical Practice Guideline for the Management of Major Depressive Disorder [VA/DoD MDD CPG] as appropriate, available at: http://www.healthquality.va.gov/guidelines/MH/mdd/)
  - Generalized anxiety disorder
  - Borderline personality disorder
  - Antisocial personality disorder
  - Posttraumatic stress disorder (PTSD) (see VA/DoD Clinical Practice Guideline for the Management of Posttraumatic Stress Disorder and Acute Stress Disorder [VA/DoD PTSD CPG], available at: http://www.healthquality.va.gov/guidelines/MH/ptsd/)
- History of drug overdose
- Under 30 years of age (see Recommendation 6)
- Co-administration of a drug capable of inducing fatal drug-drug interactions (e.g., see Recommendation 5)
- QTc interval >450 milliseconds (ms) for using methadone
- Evidence for or history of diversion of controlled substances
- Intolerance, serious adverse effects, or a history of inadequate beneficial response to opioids
- Impaired bowel motility unresponsive to therapy
- Traumatic brain injury
- Pain conditions worsened by opioids (e.g., fibromyalgia, headache)
- True allergy to opioid agents (that cannot be resolved by switching agents)

a. Significant Risk Factors

- **Duration and dose of OT:** See Recommendation 2 for more guidance on duration of OT and Recommendations 10-12 for more guidance on dosing of OT.
- **Severe respiratory instability or sleep disordered breathing:** This would include any co-occurring condition that significantly affects respiratory rate or function such as chronic obstructive pulmonary disease (COPD), asthma, pneumonia, sleep apnea, or a neuromuscular condition (e.g., amyotrophic lateral sclerosis). Two large observational studies of patients with a history of COPD and sleep apnea who were prescribed opioids showed a weak but positive association with opioid-related toxicity/overdose and overdose-related death.[58,59]
- **Acute psychiatric instability or intermediate to high acute suicide risk:** Intermediate to high acute suicide risk, severe depression, unstable bipolar disorder, or unstable psychotic disorder precludes the safe use of self-administered LOT.[60] Im et al. (2015) (n=487,462) found that a diagnosis of a mood disorder was significantly associated with suicide attempts for the chronic use of short-acting and long-acting opioids compared with no diagnosis of a mood disorder.[61]

In a study of patients on opioids, Campbell et al. (2015) reported that those with bipolar disorder had 2.9 times the odds of a suicidal ideation within the past 12 months as well as 3.2 times the odds of a lifetime suicide attempt compared to those with no bipolar disorder.[62] See Recommendation 8 and the VA/DoD Suicide CPG[2] for more information on suicidality. See the VA/DoD Clinical Practice Guideline for Management of Bipolar Disorder in Adults (VA/DoD BD CPG) for more information on bipolar disorder.[3] Merrill and colleagues found that high dose chronic opioid therapy for pain was associated with depressed mood.[63] Treatment for chronic pain with movement, exercise and cognitive-behavioral therapy for pain may have benefit in treating depression, PTSD, and in reducing suicide risk.[64]

- **Mental health disorders:**
  - **Current or history of SUD:** For patients with untreated SUD, see Recommendation 4. For patients with diagnosed OUD, see Recommendation 17. Frequent requests for early refills or atypically large quantities required to control pain can signal an emerging SUD as well as diversion (see Evidence for or history of diversion of controlled substances). See the VA/DoD SUD CPG.[4]
  - **Depression or history of depression:** Zedler et al. (2014) reported that among patients being treated by the VHA system that received opioids, a history of depression was significantly associated with opioid-related toxicity/overdose compared to no history of depression.[58] LOT has been associated with worsening depressive symptoms.[63] See the VA/DoD MDD CPG.[5]
  - **PTSD:** Seal et al. (2012) (n=15,676) noted that among patients on OT, a prevalence of self-inflicted injuries was significantly higher among patients with a history of PTSD (with or without other mental health diagnoses) as compared to patients with other (or no) mental health diagnoses.[65] For more information, see the VA/DoD PTSD CPG.[6]
- **History of drug overdose:** A history of overdose is a red flag and providers should proceed with utmost caution when considering LOT for these patients.
- **Under 30 years of age:** See Recommendation 6.

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[2] See the VA/DoD Clinical Practice Guideline for Assessment and Management of Patients at Risk of Suicide. Available at: http://www.healthquality.va.gov/guidelines/MH/srb/

[3] See the VA/DoD Clinical Practice Guideline for Management of Bipolar Disorder in Adults. Available at: http://www.healthquality.va.gov/guidelines/MH/bd/

[4] See the VA/DoD Clinical Practice Guideline for the Management of Substance Use Disorders. Available at: http://www.healthquality.va.gov/guidelines/mh/sud/index.asp.

[5] See the VA/DoD Clinical Practice Guideline for the Management of Major Depressive Disorder. Available at: http://www.healthquality.va.gov/guidelines/MH/mdd/

[6] See the VA/DoD Clinical Practice Guideline for the Management of Posttraumatic Stress Disorder and Acute Stress Disorder. Available at: http://www.healthquality.va.gov/guidelines/MH/ptsd/

- **Co-administration of a drug capable of inducing fatal drug-drug interactions:** Providers should carefully rule out and avoid potential drug interactions prior to initiating LOT. For example, the following combinations are dangerous:[66]
  - Opioids with benzodiazepines (compared to patients with no prescription, the odds ratio [OR] and 95% confidence interval [CI] for drug-related death was OR: 14.92, 95% CI: 7.00-31.77 for patients who filled a prescription for opioids and benzodiazepines; OR: 3.40, 95% CI: 1.60-7.21 for patients who filled only an opioid prescription, and 7.21, 95% CI: 3.33-15.60 for patients who filled only a benzodiazepine prescription) (see Recommendation 5) [66,67]
  - Fentanyl with CYP3A4 inhibitors
  - Methadone with drugs that can prolong the QT interval (the heart rate's corrected time interval from the start of the Q wave to the end of the T wave) (e.g., CYP450 2B6 inhibitors)
- **QTc interval >450 ms for using methadone:** Unlike most other commonly used opioids, methadone has unique pharmacodynamic properties that can prolong the QTc interval (the heart rate's corrected time interval from the start of the Q wave to the end of the T wave) and precipitate torsades de pointes, a dangerous or fatal cardiac arrhythmia. Patients who may be at risk include those with other risk factors for QTc prolongation, current or prior electrocardiograms (ECGs) with a prolonged QTc >450 ms, or a history of syncope. Therefore, ECGs before and after initiating methadone are highly advised (see Methadone Dosing Guidance).
- **Evidence for or history of diversion of controlled substances:** The clinician should communicate to patients that drug diversion is a crime and constitutes an absolute contraindication to prescribing additional medications. Because suspicion is subjective and may be based on impression, bias, or prejudice, it is important that providers who suspect diversion base treatment plans on objective evidence. Suspicions may be confirmed by a negative mass spectrometry/liquid chromatography UDT for the substance being prescribed in the absence of withdrawal symptoms in someone who is receiving opioids. A negative UDT for the prescribed opioid could also by itself be a sign of diversion. Signs of diversion may also include frequent requests for early refills or atypically large quantities required to control pain. Routine UDT, however, may not reliably detect synthetic opioids (e.g., methadone, fentanyl, tramadol) or semi-synthetic opioids (e.g., oxycodone, hydrocodone, hydromorphone). When there is evidence that the patient is diverting opioids, discontinue opioids according to Recommendations 14 and 15 and assess for underlying OUD and/or psychiatric comorbidities. Consultation with a pain specialist, psychiatrist, or SUD specialist may be warranted. Also consider consultation with local risk management and/or counsel. For patients with OUD, keep in mind that sudden discontinuation of opioids due to suspected diversion may place them at high risk for illicit opioid use and resulting opioid overdose (see Recommendation 17).
- **Intolerance, serious adverse effects, or a history of inadequate beneficial response to opioids:** Serious harm may occur should patients be prescribed additional (or different) opioids if prior administration of opioids led to serious adverse effects or was not tolerated. It is also inadvisable to prescribe opioids to patients who already have had an adequate opioid trial (of

sufficient dose and duration to determine whether or not it will optimize benefit) without a positive response.

- **Impaired bowel motility unresponsive to therapy:** Opioids inhibit bowel peristalsis. Their use with patients with impaired bowel motility can increase the risk of severe constipation/impaction or possible obstruction.
- **Headache not responsive to other pain treatment modalities:** LOT is an ineffective treatment modality for patients with migraine headaches (with or without aura), tension-type headaches, occipital neuralgia, or myofascial pain and may result in worsening of the underlying headache condition through factors such as central sensitization and withdrawal.
- **Traumatic brain injury (TBI):** Patients with a history of TBI who use chronic short-acting and long-acting opioids are more likely to attempt suicide.[61]
- **True allergy to opioid agents:** Morphine causes a release of histamine that frequently results in itching, but this does not constitute an allergic reaction. True allergy to opioid agents (e.g., anaphylaxis) is not common, but does occur. Generally, allergy to one opioid does not mean the patient is allergic to other opioids; many times, rotating to a different opioid may be effective. When an opioid allergy is present and OT is being considered, consultation with an allergist may be helpful.

VI. About this Clinical Practice Guideline

This OT CPG is in line with the efforts described above to improve our understanding and treatment of pain, as well as to mitigate the inappropriate prescribing and ill effects of opioids. It is intended for VA and DoD healthcare practitioners including physicians, nurse practitioners, physician assistants, physical and occupational therapists, psychologists, social workers, nurses, clinical pharmacists, chaplains, addiction counselors, and others involved in the care of Service Members and their beneficiaries, retirees and their beneficiaries, or Veterans on or being considered for LOT. In conjunction with other efforts already under way, this CPG is aimed at improving safe and appropriate prescribing and use of opioids to treat chronic pain.

As with other CPGs, there are limitations, including significant evidence gaps. Further, there is a need to develop effective strategies for guideline implementation and evaluation of the effect of guideline adherence on clinical outcomes. Thus, as stated in the qualifying statements at the beginning of the CPG, this CPG is not intended to serve as a standard of care. Standards of care are determined on the basis of all clinical data available for an individual patient and are subject to change as scientific knowledge and technology advance and patterns evolve. This CPG is based on evidence available by December 2016 and is intended to provide a general guide to best practices. The guideline can assist healthcare providers, but the use of a CPG must always be considered as a recommendation, within the context of a provider's clinical judgment and patient values and preferences, for the care of an individual patient.

A. Scope of this Clinical Practice Guideline

This OT CPG is designed to assist healthcare providers in managing or co-managing patients on or being considered for LOT. Specifically, this CPG is intended for adults, including Veterans as well as deployed and non-deployed Active Duty Service Members, their beneficiaries, and retirees and their beneficiaries, with chronic pain who are receiving care from the VA or DoD healthcare delivery systems. This CPG is not intended for and does not provide recommendations for the management of pain with LOT in children or adolescents, in patients with acute pain, or in patients receiving end-of-life care. As is so for any pharmacotherapy, any decision about prescribing opioids, or alternative medications for pain, for pregnant women should be made with due caution and cognizance of applicable U.S. Food and Drug Administration (FDA) labeling. Any patient in the VA or DoD healthcare system should be offered access to the interventions that are recommended in this guideline after taking into consideration the patient's specific circumstances.

While these guidelines are broadly recommended, their implementation is intended to be patient-centered. Thus, treatment and care should take into account a patient's needs and preferences. Good communication between healthcare professionals and the patient about the patient's pain experience, treatment goals, and challenges is essential and should be guided by evidence-based information tailored to the patient's needs. An empathetic and non-judgmental (versus a confrontational or adversarial) approach to communication with a patient is highly recommended in order to build trust and facilitate frank discussions relating to the social, economic, emotional, and cultural factors that influence patients' perceptions, behaviors, and decision making.

The information that patients are given about treatment and care should be culturally appropriate and also available to people with limited literacy skills. It should also be accessible to people with additional

needs such as physical, sensory, or learning disabilities. Family involvement should be considered if appropriate.

The systematic review conducted for the update of this CPG encompassed interventional studies (primarily randomized controlled trials [RCTs]) published between March 2009 and December 2016 and targeted nine key questions (KQs) focusing on the means by which the delivery of healthcare could be optimized for patients on or being considered for LOT. Because a comprehensive review of the evidence related to LOT was not feasible, the nine selected KQs were prioritized from many possible KQs. Therefore, many of the 2010 OT CPG recommendations were considered for inclusion in the updated version of the guideline without an updated review of the evidence. The section on Recommendations delineates whether or not the current CPG recommendations were based on an updated evidence review. Appendix H delineates whether the 2010 OT CPG recommendations were considered for inclusion in the update based on an updated evidence review or based on the evidence included in the 2010 OT CPG. The section on Recommendation Categorization further describes the methodology used for the categorization.

B. Highlighted Features of this Clinical Practice Guideline

The 2017 version of the VA/DoD OT CPG is the second update to the original CPG. It provides practice recommendations for the care of populations with chronic pain already on or being considered for LOT. Although there are many other approaches to the treatment of chronic pain, the scope of this CPG is to focus on the use of opioids for chronic pain rather than being comprehensive about all treatment options. A particular strength of this CPG is the multidisciplinary stakeholder involvement from its inception, ensuring representation from the broad spectrum of clinicians engaged in the treatment and management of patients with chronic pain on or being considered for LOT.

The framework for recommendations in this CPG considered factors beyond the strength of the evidence, including balancing desired outcomes with potential harms of treatment, equity of resource availability, the potential for variation in patient values and preferences, and other considerations (see Methods for more information). Applicability of the evidence to VA/DoD populations was also taken into consideration. A structured algorithm (see Algorithm) accompanies the guideline to provide an overview of the recommendations in the context of the flow of patient care and clinician decision making and to assist with training providers. The algorithm may be used to help facilitate translation of guideline recommendations into effective practice.

C. Methods

The current document is an update to the 2010 *VA/DoD Clinical Practice Guideline for the Management of Opioid Therapy for Chronic Pain*. The methodology used in developing the 2017 CPG follows the VA/DoD Guideline for Guidelines,[1] an internal document of the VA and DoD EBPWG. The VA/DoD Guideline for Guidelines can be downloaded from http://www.healthquality.va.gov/policy/index.asp. This document provides information regarding the process of developing guidelines, including the identification and assembly of the Guideline Champions ("Champions") and other subject matter experts from within the VA and DoD, known as the "Work Group," and ultimately, the development and submission of an updated OT CPG. The VA Office of Quality, Safety and Value, in collaboration with the Office of Evidence Based Practice, U.S. Army Medical Command, the proponent for CPGs for the DoD, identified two clinical leaders,

Jack Rosenberg, MD, FASAM from the VA and Christopher Spevak, MD, MPH, JD from the DoD, as Champions for the 2017 CPG.

The Champions and Work Group for this CPG were charged with developing evidence-based clinical practice recommendations and writing and publishing a guideline document to be used by providers within the VA and DoD healthcare systems. Specifically, the Champions and the Work Group were responsible for identifying the KQs – those considered most clinically relevant, important, and interesting with respect to the management of patients with chronic pain on or being considered for LOT. The Champions and the Work Group also provided direction on inclusion and exclusion criteria for the evidence review and assessed the level and quality of the evidence. The amount of new scientific evidence that had accumulated since the previous version of the CPG was taken into consideration in the identification of the KQs. In addition, the Champions assisted in:

- Identifying appropriate disciplines of individuals to be included as part of the Work Group
- Directing and coordinating the Work Group
- Participating throughout the guideline development and review processes

The Lewin Team, including The Lewin Group, Duty First Consulting, ECRI Institute, and Sigma Health Consulting, LLC, was contracted by the VA and DoD to support the development of this CPG and conduct the evidence review. The first conference call was held in October 2015, with participation from the contracting officer's representative (COR), leaders from the VA Office of Quality, Safety and Value and the DoD Office of Evidence Based Practice, and the Champions. During this call, participants discussed the scope of the guideline initiative, the roles and responsibilities of the Champions, the project timeline, and the approach for developing and prioritizing specific research questions on which to base a systematic review about the management of LOT. The group also identified a list of clinical specialties and areas of expertise that were important and relevant to the management of LOT, from which Work Group members were recruited. The specialties and clinical areas of interest included: Anesthesiology, Addictive Disorders and Addiction Medicine, Clinical Neurophysiology, Family Medicine, Geriatrics, Internal Medicine, Mental/Behavioral Health, Neurology, Nursing, Pain Management, Pain Medicine, Pain Psychology, Palliative Care, Pharmacy, Physical Medicine and Rehabilitation, Physical Therapy, Primary Care, Psychiatry, Psychology, and Social Work.

The guideline development process for the 2017 CPG update consisted of the following steps:

1. Formulating and prioritizing KQs (or evidence questions)
2. Conducting the systematic review of the literature
3. Convening a face-to-face meeting with the CPG Champions and Work Group
4. Drafting, revising, and submitting a final CPG about the management of LOT to the VA/DoD EBPWG

Appendix E provides a detailed description of each of these tasks.

b. Grading Recommendations

The Champions and Work Group used the GRADE system to assess the quality of the evidence base and assign a grade for the strength for each recommendation. The GRADE system uses the following four domains to assess the strength of each recommendation:[68]

- Confidence in the quality of the evidence
- Balance of desirable and undesirable outcomes
- Patient or provider values and preferences
- Other implications, as appropriate, e.g.,:
  - Resource use
  - Equity
  - Acceptability
  - Feasibility
  - Subgroup considerations

Using this system, the Champions and Work Group determined the direction (for or against) and relative strength (strong or weak) of each recommendation.[68] The direction indicates that the desirable effects of the recommendation outweigh the undesirable effects of the recommendation (for) or that the opposite is true (against). The strength indicates the Work Group's level of confidence in the balance of desirable and undesirable effects of the recommendation among the intended patient population.[69] A strong recommendation indicates the Work Group is confident in this balance (e.g., that the desirable effects outweigh the undesirable effects). A weak recommendation indicates that the balance is still likely, but the Work Group's confidence in the balance is lower than for a strong recommendation.

Using these elements, the grade of each recommendation is presented as part of a continuum:

- Strong For (or "We recommend offering this option …")
- Weak For (or "We suggest offering this option …")
- Weak Against (or "We suggest not offering this option …")
- Strong Against (or "We recommend against offering this option …")

The grade of each recommendation made in the 2017 OT CPG can be found in Recommendations. Additional information regarding the use of the GRADE system can be found in Grading Recommendations.

c. Reconciling 2010 Clinical Practice Guideline Recommendations

Evidence-based CPGs should be current, which typically requires revisions of previous guidelines based on new evidence or as scheduled, subject to time-based expirations.[70] For example, the United States Preventive Services Task Force (USPSTF) has a process for refining or otherwise updating its recommendations pertaining to preventive services.[71] Further, the inclusion criteria for the National Guideline Clearinghouse specify that a guideline must have been developed, reviewed, or revised within the past five years.

The 2017 OT CPG is an update of the 2010 CPG. Thus, the structure and content of the 2017 CPG is reflective of the previous version of the CPG, but modified where necessary to reflect new evidence and new clinical priorities.

The Work Group focused largely on developing new and updated recommendations based on the evidence review conducted for the priority areas addressed by the KQs. In addition to those new and updated recommendations, the Work Group considered the current applicability of other recommendations that were included in the previous 2010 OT CPG without complete review of the relevant evidence, subject to evolving practice in today's environment.

To indicate which recommendations were developed based on the updated review of the evidence versus recommendations that were carried forward from the 2010 version of the CPG, a set of recommendation categories was adapted from those used by the National Institute for Health and Care Excellence (NICE).[72,73] These categories, along with their corresponding definitions, were used to account for the various ways in which older recommendations could have been updated. In brief, the categories took into account whether or not the evidence that related to a recommendation was systematically reviewed, the degree to which the recommendation was modified, and the degree to which a recommendation is relevant in the current patient care environment and inside the scope of the CPG. Additional information regarding these categories and their definitions can be found in the section on Recommendation Categorization. The categories for the recommendations included in the 2017 CPG can be found in the Recommendations section. The categorizations for each 2010 CPG recommendation can be found in Appendix H.

Between the development of the 2010 and 2017 versions of the OT CPG, VA/DoD adopted a new evidence rating system. The CPG Work Group recognized the need to accommodate this transition in evidence rating systems from the USPSTF system in the 2010 CPG to the GRADE system in the 2017 CPG. In order to report the strength of all recommendations using a consistent format (i.e., the GRADE system) the Work Group converted the USPSTF evidence grades accompanying the carryover recommendations from the 2010 guideline to the GRADE system. As such, the CPG Work Group considered the strength of the evidence cited for each recommendation in the 2010 OT CPG as well as harms and benefits, values and preferences, and other implications, where possible.

In cases where a 2010 OT CPG recommendation was covered by a 2017 KQ, peer-reviewed literature published since the 2010 OT CPG was considered along with the evidence base used for the 2010 CPG. Where new literature was considered in converting the strength of the recommendation from the USPSTF to the GRADE system, it is referenced in the discussion following the corresponding recommendation, as well as in Appendix G.

The CPG Work Group recognizes that, while there are practical reasons for incorporating findings from a previous systematic review, previous recommendations, or recent peer-reviewed publications into an updated CPG, doing so does not involve an original, comprehensive systematic review and, therefore, may introduce bias.[74]

d. Peer Review Process

The CPG was developed through an iterative process in which the Work Group produced multiple drafts of the CPG. The process for developing the initial draft is described in more detail in Drafting and Submitting the Final Clinical Practice Guideline.

Once a near-final draft of the guideline was agreed upon by the Champions and Work Group, the draft was sent out for peer review and comment. The draft was posted on a wiki website for a period of 14 business days. The peer reviewers comprised individuals working within the VA and DoD health systems as well as experts from relevant outside organizations designated by the Work Group. External organizations that participated in the peer review included the following:

- American Academy of Addiction Psychiatry (AAAP)
- American Academy of Pain Medicine (AAPM)
- American Physical Therapy Association (APTA)
- American Society of Addiction Medicine (ASAM)
- University of Kentucky
- University of Minnesota

VA and DoD Leadership reached out to both the internal and external peer reviewers to solicit their feedback on the CPG. Reviewers were provided a hyperlink to the wiki website where the draft CPG was posted. For transparency, all reviewer feedback was posted in tabular form on the wiki site, along with the name of the reviewer. All feedback from the peer reviewers was discussed and considered by the Work Group. Modifications made throughout the CPG development process were made in accordance with the evidence.

D. Implementation

This CPG, including its recommendations and algorithm, is designed to be adapted by healthcare providers for the treatment of individual patients, bearing in mind patient-level considerations as well as local needs and resources. The algorithm serves as a tool to prompt providers to consider key decision points in the course of care.

Although this CPG represents the recommended practice on the date of its publication, medical practice is evolving and this evolution requires continuous updating based on published information. New technology and more research will improve patient care in the future. Identifying areas where evidence was lacking for the 2017 CPG can help identify priority areas for future research. Future studies examining the results of OT CPG implementation may lead to the development of new evidence particularly relevant to clinical practice.

E. Summary of Patient Focus Group Methods and Findings

When forming guideline recommendations, consideration should be given to the values of those most affected by the recommendations: patients. Patients bring perspectives, values, and preferences into their healthcare experience, and more specifically their pain care experience, that can vary from those of clinicians. These differences can affect decision making in various situations, and should thus be

highlighted and made explicit due to their potential to influence a recommendation's implementation.[75,76] Focus groups can be used as an efficient method to explore ideas and perspectives of a group of individuals with an *a priori* set of assumptions or hypotheses and collect qualitative data on a thoughtfully predetermined set of questions.

Therefore, as part of the effort to update this CPG, VA and DoD Leadership, along with the OT CPG Work Group, held a patient focus group on December 14, 2015, at the Washington DC VA Medical Center. One additional family caregiver was interviewed separately at a later date. The aim of the focus group and interview was to further the understanding of the perspectives of patients receiving OT within the VA and/or DoD healthcare systems. The focus group and interview explored patient perspectives on a set of topics related to management of OT in the VA and DoD healthcare systems, including knowledge of OT and other pain treatment options, delivery of care, and the impact of and challenges with OT and chronic pain.

It is important to note the focus group was a convenience sample and the Work Group recognizes the limitations inherent in the small sample size. Less than 10 people were included in the focus group consistent with the requirements of the federal Paperwork Reduction Act, 1980. The Work Group acknowledges that the sample of patients included in this focus group may not be representative of all VA and DoD patients on or being considered for OT for chronic pain. Further, time limitations for the focus group prevented exhaustive exploration of all topics related to pain care in the VA and DoD and the patients' broader experiences with their care. Thus, the Work Group made decisions regarding the priority of topics to discuss at the focus group and interview. These limitations, as well as others, were considered as the information collected from the discussion was used for guideline development. Recruitment for participation in the focus group was managed by the Champions and VA and DoD Leadership, with assistance from coordinators at the facility at which the focus group took place.

The following concepts are ideas and suggestions about aspects of care that are important to patients and family caregivers and that emerged from the discussion. These concepts were needed and important parts of the participants' care and added to the Work Group's understanding of patient values and perspectives. Additional details regarding the patient focus group methods and findings can be found in Appendix F.

OT CPG Focus Group Concepts	
A.	Using shared decision making, consider all treatment options and develop treatment plan based on the balance of risks, benefits, and patient-specific goals, values, and preferences
B.	Modify treatment based on patient response, considering patient-specific goals, values, and preferences
C.	Involve family caregivers in accordance with patient preferences and maintain open, trusting, and respectful relationship with patients and family caregivers
D.	Educate patients regarding treatment plan, alternative treatment options, and monitoring
E.	Within and between healthcare systems, work with appropriate providers to ensure continuity of high quality care
F.	Organize treatment to encourage patient adherence and participation
G.	Acknowledge and minimize effects of potential medical error and take action to prevent future medical error

F. Conflict of Interest

At the start of this guideline development process and at other key points throughout, the project team was required to submit disclosure statements to reveal any areas of potential conflict of interest (COI) in

the past 24 months. Verbal affirmations of no COI were also used as necessary during meetings throughout the guideline development process. The project team was also subject to random web-based surveillance (e.g., ProPublica).

If a project team member reported a COI (actual or potential), measures were in place to mitigate the introduction of bias into the guideline development process. Identified COIs would be reported to the Office of Evidence Based Practice and disclosed to the CPG Work Group in tandem with their review of the evidence and development of recommendations. The Office of Evidence Based Practice and the OT CPG Work Group would then determine whether or not action, such as restricting participation and/or voting on sections related to the conflict or removal from the Work Group, was necessary. If deemed necessary, action would have been taken by the co-chairs and the Office of Evidence Based Practice, based on the level and extent of involvement, to mitigate the COI.

No OT CPG Work Group members reported relationships and/or affiliations which had the potential to introduce bias; thus, no further action was taken to mitigate COIs for this particular CPG.

G. Patient-centered Care

VA/DoD CPGs encourage clinicians to use a patient-centered care approach that is tailored to the patient's capabilities, needs, goals, prior treatment experience, and preferences. Regardless of setting, all patients in the healthcare system should be offered access to evidence-based interventions appropriate to that patient. When properly executed, patient-centered care may decrease patient anxiety, increase trust in clinicians,[77] and improve treatment adherence.[78] Improved patient-clinician communication through patient-centered care can be used to convey openness to discuss any future concerns.

As part of the patient-centered care approach, clinicians should review the patient's history including previous treatment approaches, their results, and any other outcomes with the patient. They should ask the patient about his or her willingness to accept a referral to an addiction or other behavioral health specialist when appropriate. Lastly, they should involve the patient in prioritizing problems to be addressed and in setting specific goals regardless of the selected setting or level of care. The below approach may be used in setting SMART (Specific, Measurable, Action Oriented, Realistic, Timed) goals for the patient (Table 1).

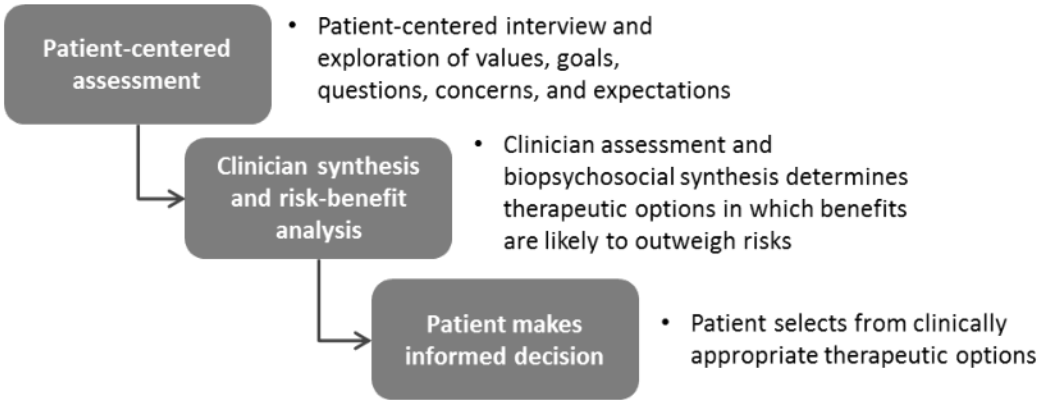
Table 1. Guide in Setting SMART Goals [79]

Specific	A goal should be clear and concise. It is difficult to know when action toward a goal has been started and when it has been completed if it is not specific.
Measurable	A goal should be measurable so that Veterans can track their progress. Veterans need to have clear criteria for progress and completion when taking action on a goal. Keeping tabs on progress can be inspiring.
Action Oriented	A goal should include action. And that action should be in direct control of the Veteran.
Realistic	A goal should be largely within the reach of the Veterans. It is best to work on small lifestyle changes that are doable. Avoid the pitfalls of having Veterans see only the big picture and not the small steps.
Timed	A goal should be tied to a timetable for completing specific, measurable and realistic action.

H. Shared Decision Making

The shared decision making process for chronic pain treatment planning is based on the foundation of a patient-centered assessment of risks and benefits and a clinical synthesis performed by the provider (Figure 1). The patient-centered assessment incorporates a patient-centered interview, and exploration of patient values, goals, questions, concerns, and expectations. Next, the clinician performs a biopsychosocial assessment and determines clinically appropriate therapeutic options in which benefits are likely to outweigh risks. The process culminates in a shared decision making process to develop a patient-centered treatment plan by the patient selecting from the clinically appropriate treatment options generated in the first two steps.

Figure 1. Shared Decision Making for Chronic Pain Treatment and Long-Term Opioid Therapy

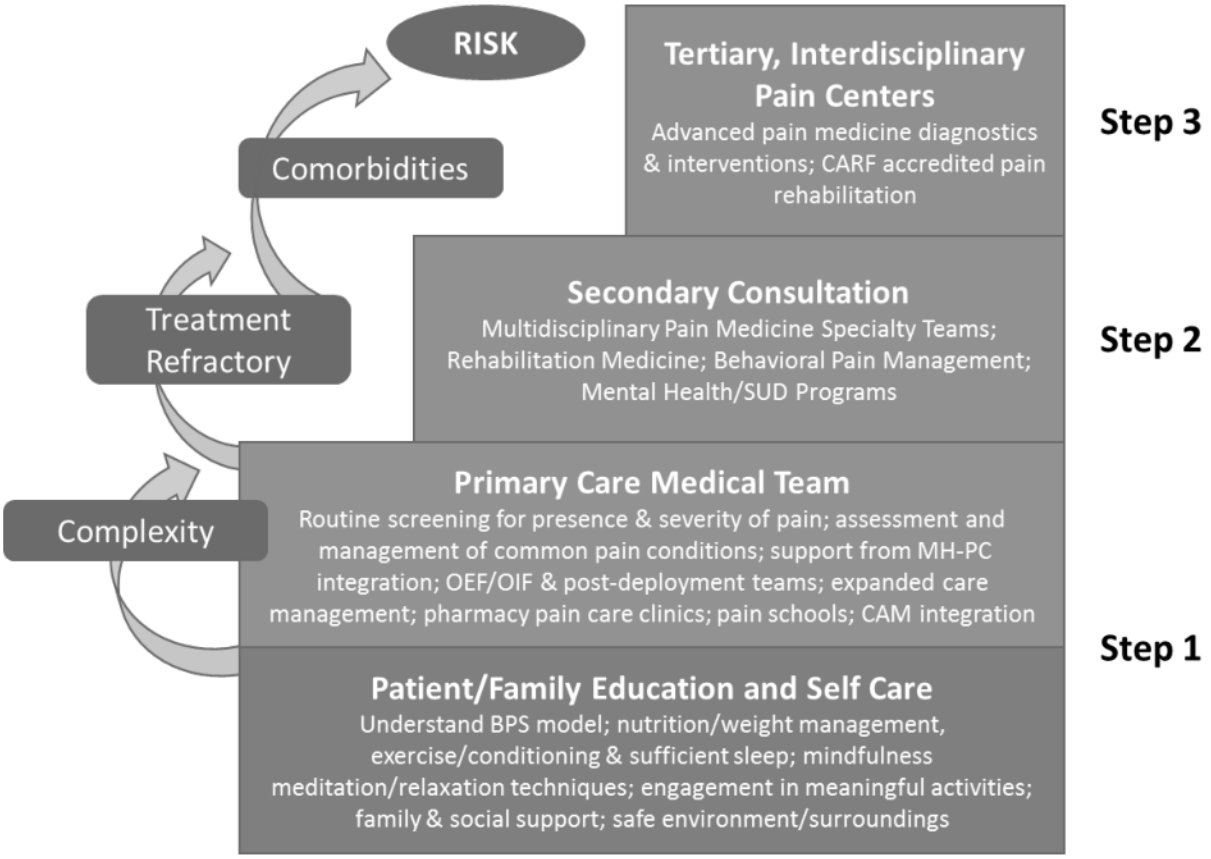

Patient-centered assessment
• Patient-centered interview and exploration of values, goals, questions, concerns, and expectations
Clinician synthesis and risk-benefit analysis
• Clinician assessment and biopsychosocial synthesis determines therapeutic options in which benefits are likely to outweigh risks
Patient makes informed decision
• Patient selects from clinically appropriate therapeutic options

I. Stepped Care Model for Pain Management

The Stepped Care Model for Pain Management, developed by VA, has been implemented within both the VHA and Military Health System (MHS) with the aim of providing a continuum of effective, coordinated, and patient-centered treatment to patients with pain. With education, self-care, and whole-health approaches to wellness as the foundation, this model provides progressively more intensive biopsychosocial care within increasingly specialized settings as patients become more complex, have a greater degree of comorbidity, and present higher risk. Psychological, physical, complementary and

alternative, and medication therapies are often combined to create a multimodal pain care plan. The goals of the Stepped Care Model for Pain Management include functional rehabilitation, improvement in quality of life, and prevention of the pain becoming chronic and associated deterioration in function (Figure 2).

Figure 2. Stepped Care Model for Pain Management*


RISK
Comorbidities
Treatment Refractory
Complexity
Tertiary, Interdisciplinary Pain Centers
Advanced pain medicine diagnostics & interventions; CARF accredited pain rehabilitation
Step 3
Secondary Consultation
Multidisciplinary Pain Medicine Specialty Teams; Rehabilitation Medicine; Behavioral Pain Management; Mental Health/SUD Programs
Step 2
Primary Care Medical Team
Routine screening for presence & severity of pain; assessment and management of common pain conditions; support from MH-PC integration; OEF/OIF & post-deployment teams; expanded care management; pharmacy pain care clinics; pain schools; CAM integration
Step 1
Patient/Family Education and Self Care
Understand BPS model; nutrition/weight management, exercise/conditioning & sufficient sleep; mindfulness meditation/relaxation techniques; engagement in meaningful activities; family & social support; safe environment/surroundings

*Adapted from the Interagency Pain Research Coordinating Committee's National Pain Strategy (2016) [26]
Abbreviations: BPS: biopsychosocial; CAM: complementary and alternative medicine; CARF: Commission on Accreditation of Rehabilitation Facilities; MH-PC: Primary Care-Mental Health; OEF: Operation Enduring Freedom; OIF: Operation Iraqi Freedom; PACT: Patient Aligned Care Team; SUD: substance use disorders

J. Transfer of Care

As the entire medical community is moving toward a greater understanding of the need for opioid safety, it is possible that a provider may receive, as a result of a transfer of care, a patient on a high-risk opioid regimen that raises concerns related to the provider's and patient's current understanding of opioid risks. Some universal approaches should be used in the management of care for the patient regardless of the location from which that patient is transferred.

- Clinicians should provide each new patient with a full evaluation, understanding that chronic pain is a complex process that requires a comprehensive assessment of the whole individual as well as their social circumstances. The general goals of the interview with the patient are to do more than just gather information. This process should build a therapeutic relationship as well as facilitate behavior change when necessary. It is important to understand the situation from

the patient's perspective, elicit a pain-specific history to aid in establishing the correct pain diagnosis, identify patient-specific coping strategies, identify patient-specific pain interference with functioning, and identify important co-occurring conditions. The transferring provider should also communicate the patient's medical history to the receiving provider to ensure it is taken into account along with the patient's perspective. This can aid the clinician in synthesizing the full biopsychosocial story.

- Clinicians should review previous medical records to determine what diagnostic and therapeutic options have already been tried. In addition, previous medical records can help to determine the patient's risk of a non-overdose opioid-related adverse event, overdose risk, and risk of having developed or developing OUD. It can also help to determine co-occurring conditions that will need to be evaluated and treated in order to put together a comprehensive approach to this patient's pain.
- Clinicians should determine what the patient knows about current concerns related to OT and how comfortable he or she is with an approach that will be addressing opioid safety along with an integrated whole person approach to pain. Each patient may arrive from other providers with a different understanding of the current concerns related to OT, and educational gaps will need to be acknowledged and addressed.
- Clinicians should offer all new patients a physical exam to help to determine the cause of the pain as well as co-occurring conditions that may complicate pain symptoms and/or treatment.
- Clinicians should provide each patient an assessment that outlines the specifics related to opioid safety.
  - What is the diagnosis for which opioids are prescribed?
  - What non-opioid therapies have been trialed and/or is the patient currently using?
  - Are there co-occurring conditions or medication doses/combinations that would increase the risk of OT?
- Clinicians should use standard opioid risk mitigation strategies such as checking the Prescription Drug Monitoring Programs (PDMPs); making sure the patient has participated in shared-decision making about OT and signed and understands the opioid informed consent (see Appendix A); obtaining consent for and performing a UDT (see Appendix B); and offering OEND. See Recommendation 7 for more information on risk mitigation.

One frequently asked question is how to proceed when a patient requests to transfer an opioid prescription that the receiving provider has determined to be too risky to continue. For patients transferred from within the VA and/or DoD system, clinicians should employ risk stratified tapering strategies (see Recommendations 14 and 15). Clinicians should engage patients in shared decision making including consideration of the patient's values, goals, concerns, and preferences prior to tapering. It is also important that clinicians asses for and treat OUD when present (see Recommendation 17).

For patients who are transferring from outside of the VA and/or DoD, there may be some unique issues to consider.

- Are complete medical records available that would inform treatment planning? Until full record review and communication with the previous prescriber are completed, there are significant risks of taking over opioid prescribing even if it is with intent to taper.
- Has the new plan of care been communicated to the previous prescriber and the patient? If it is felt that the regimen is too risky to take over the management with the resources available, then it is important to communicate this to the patient as well as the previous prescriber so that they can begin an exit plan for the patient as indicated. If the new provider feels comfortable taking over the OT, even if it is to start a taper, then this needs to be communicated to the previous prescriber as soon as possible to avoid duplication of prescriptions.

K. Clinical Decision Support Tools

There are electronic tools to facilitate clinical risk assessment and adherence to risk mitigation. Two tools currently used in the VA are the Opioid Therapy Risk Report (OTRR) and the Stratification Tool for Opioid Risk Mitigation (STORM). The OTRR allows VA providers to review clinical data related to opioid pain treatment within the electronic medical record (EMR), providing an efficient way of monitoring the data. The STORM tool incorporates co-occurring medical and mental health conditions, SUD, opioid dose, co-prescribed sedatives, and information about prior adverse events and generates estimates of patients' risk or hypothetical risk when considering initiation of opioid therapy. It quantifies risk for poisoning or suicide-related events and for drug-related events, accidents, falls, and drug-induced conditions over a three-year window. Further, it provides suggestions as to what alternative treatments have not been tried and what risk mitigation strategies need to be applied. Evidence supporting their use is poor but they facilitate providers' determination of current, past and potential therapies and strategies.

VII. Guideline Work Group

Guideline Work Group*	
Department of Veterans Affairs	***Department of Defense***
Jack Rosenberg, MD, FASAM (Champion)	**Christopher Spevak, MD, MPH, JD (Champion)**
Michael O. Chaffman, PharmD, BCPS	Elizabeth Rees Atayde, RN, MSN, FNP, CCM, CPHM
Karen Drexler, MD	LTC Robert Brutcher, PharmD, PhD
Franz Macedo, DO	Corinne Devlin, MSN, RN, FNP-BC
Aram Mardian, MD	LTC William Grief, MD
Anthony J. Mariano, PhD	James Hardin, LCSW-C, MAC
Ilene Robeck, MD	Connie Kurihara, RN
Friedhelm Sandbrink, MD	CDR Marisol Martinez, PharmD, MBA
Maria Silveira, MD, MA, MPH	Capt Erick C. Messler, PhD
Nancy Wiedemer, MSN, RN, ANP-BC	LTC Jason Silvernail, DPT, DSc, FAAOMPT
	CAPT Necia Williams, MD
Office of Quality, Safety and Value Veterans Health Administration	***Office of Evidence Based Practice U.S. Army Medical Command***
Eric Rodgers, PhD, FNP-BC James Sall, PhD, FNP-BC Rene Sutton, BS, HCA	Corinne K. B. Devlin, MSN, RN, FNP-BC
Lewin Group	***ECRI Institute***
Clifford Goodman, PhD Christine Jones, MS, MPH, PMP Erika Beam, MS Anjali Jain, MD	Kristen E. D'Anci, PhD Nancy M. Sullivan, BA James Reston, PhD, MPH Mrin Joshi, MS Erin Payne, MS Raj Stewart, PhD Stacey Uhl, MS Allison Gross, MLS
Sigma Health Consulting, LLC	***Duty First Consulting***
Frances Murphy, MD, MPH	Anita Ramanathan, BA Megan McGovern, BA

*Additional contributor contact information is available in Appendix I.

VIII. Discussion of Recommendations

A. Initiation and Continuation of Opioids

Recommendation

1. a) We recommend against initiation of long-term opioid therapy for chronic pain. **(Strong against)**
   b) We recommend alternatives to opioid therapy such as self-management strategies and other non-pharmacological treatments. **(Strong for)**
   c) When pharmacologic therapies are used, we recommend non-opioids over opioids. **(Strong for)**
   (Reviewed, New-replaced)

Discussion

As outlined in this CPG, there is a rapidly growing understanding of the significant harms of LOT even at doses lower than 50 mg oral morphine equivalent daily dose [MEDD], including but not limited to overdose and OUD. At the same time there is a lack of high quality evidence that LOT improves pain, function, and/or quality of life. The literature review conducted for this CPG identified no studies evaluating the effectiveness of LOT for outcomes lasting longer than 16 weeks. Given the lack of evidence showing sustained functional benefit of LOT and moderate evidence outlining harms, non-opioid treatments are preferred for chronic pain. Patient values, goals, concerns, and preferences must be factored into clinical decision making on a case-by-case basis. When considering the initiation or continuation of LOT, it is important to consider whether LOT will result in clinically meaningful improvements in function such as readiness to return to work/duty and/or measurable improvement in other areas of function, such that the benefits outweigh the potential harms.

While there is currently no evidence in the literature documenting the benefit of LOT that demonstrates improvement in pain and function, we recognize that in a rare subset of individuals a decision to initiate LOT may be considered (e.g., for intermittent severe exacerbations of chronic painful conditions). If a decision is made to initiate LOT, a careful assessment of benefits and risks should be made to ensure that the benefits are expected to outweigh the well-documented risks. In addition, prior to this consideration, a multimodal treatment plan should be integrated into the patient's care. Once opioid therapy is initiated, all opioid risk mitigation strategies outlined in this guideline (see Recommendation 7) should be put into place.

In 2011, in response to the recognition of pain and its management as a public health problem, the National Academy of Medicine investigated and reported on the state of pain research, treatment, and education in the U.S. The report called for a cultural transformation in the way pain is viewed and treated.[3] Accordingly, the U.S. Department of Health and Human Services (HHS) National Pain Strategy (March 2016) recommends a biopsychosocial approach to pain care that is multimodal and interdisciplinary.[26] The underlying concepts of the biopsychosocial model of pain include the idea that pain perception and its effects on the patient's function is mediated by multiple factors (e.g., mood, social support, prior experience, biomechanical factors), not just biology alone. With this overall change in construct, a biopsychosocial assessment and treatment plan should be tailored accordingly.

Psychological therapies (e.g., cognitive behavioral interventions such as Cognitive Behavioral Therapy [CBT], biofeedback) have been found to be effective for pain reduction in multiple pain conditions.[80-82]

Exercise treatments, including yoga, also have evidence of benefit for reducing pain intensity and disability when compared to usual care in the treatment of chronic pain conditions.[83-85] Exercise and psychological therapies may each exert their influence through multiple mechanisms including but not limited to the reduction in fear-avoidance, reduction in catastrophizing, and/or enhancing mood.[80] Similarly, multidisciplinary biopsychosocial rehabilitation (described as a combination of a physical intervention such as graded exercise and a psychological, social, or occupational intervention) has been shown to be more effective than usual care in improving pain and disability.[81] These interventions are safe and have not been shown to increase morbidity or mortality.

In light of the low harms associated with exercise and psychological therapies when compared with LOT these treatments are preferred over LOT, and should be offered to all patients with chronic pain including those currently receiving LOT. There is insufficient evidence to recommend psychological over physical therapies or vice versa; the choice of which to try first should be individualized based on patient assessment and a shared decision making process (see Patient Focus Group Methods and Findings).[80]

In addition to non-pharmacological therapies (e.g., exercise, CBT), appropriate mechanism and condition-specific non-opioid pharmacologic agents should be tried and optimized before consideration of opioid medications (e.g., gabapentin in neuropathic pain states).[83] Potential contraindications and long-term risks of use should be considered for non-opioid pharmacologic agents as well, as these also can carry risk of harm, depending on the specific patient and chosen medication.

Patient access to physical, psychological, and pain rehabilitation modalities should be considered. In some cases access to care may be limited; all VA and DoD clinics may not have access to multidisciplinary pain services. Still, all avenues for obtaining these treatments (e.g. Internet based CBT) and all appropriate non-opioid medications should be exhausted before consideration of LOT.[82]

Further studies may help determine earlier in the course of treatment which patients are most likely to benefit from a specific non-pharmacologic therapy (physical, psychological, and pain rehabilitation) or non-opioid pharmacologic therapies alone or as part of a multimodal approach.

Recommendations

2. If prescribing opioid therapy for patients with chronic pain, we recommend a short duration.
   (Strong for| Reviewed, New-replaced)

   Note: Consideration of opioid therapy beyond 90 days requires re-evaluation and discussion with patient of risks and benefits.

3. For patients currently on long-term opioid therapy, we recommend ongoing risk mitigation strategies (see Recommendations 7-9), assessment for opioid use disorder, and consideration for tapering when risks exceed benefits (see Recommendation 14).
   (Strong for| Reviewed, New-replaced)

Discussion

The support for these recommendations is two-fold: a paucity of research showing benefit for LOT and the strength of the evidence demonstrating the potential for life-threatening harm. Of utmost concern is the

heightened risk for developing OUD in patients who receive OT beyond 90 days (see Appendix C for Diagnostic and Statistical Manual of Mental Disorders [DSM] 5 diagnostic criteria for OUD).

Similar to other risk factors, continuing OT beyond 90 days' duration should be weighed heavily in the risk-benefit calculus for LOT. Continuing OT for longer than 90 days is not an absolute contraindication to LOT. There may be some situations where the benefits of LOT clearly outweigh the risks. That must be determined through individual clinical assessment.

Moderate quality evidence demonstrates that the prevalence of OUD in patients with CNCP is related to duration of opioid use as well as dose (see Recommendations 7-9).[86-88] There are two studies of patients with CNCP which support the current recommendations. Edlund et al. (2014) conducted a large retrospective cohort study where they examined claims data from a health insurance database between 2000 and 2005 to examine factors predictive of developing OUD.[86] Days' supply of opioids was categorized as none, acute duration (1-90 days), or chronic duration (91+ days). Average daily dose was defined as none, low (1-36 mg MEDD), medium (36-120 mg MEDD), or high (>120 mg MEDD). The OR of developing OUD ranged based on dose and duration (OR: 3.03, 95% CI: 2.32-3.95 for low dose, acute opioid prescription; OR: 14.92, 95% CI: 10.38-21.46 for low dose, chronic opioids prescriptions; OR: 3.10, 95% CI: 1.67-5.77 for high dose, acute opioid prescriptions; OR: 122.45, 95% CI: 72.79-205.99 for high dose, chronic opioid prescriptions). They found that even greater than opioid dose, duration of OT was the strongest predictor of developing OUD. Additionally, a study by Boscarino et al. (2011) examined medical records from a large healthcare system.[89] Through interviews with a random sample of patients on LOT, they examined factors associated with and the prevalence of OUD (using DSM IV and 5 criteria). These results showed that the prevalence of lifetime OUD for patients on LOT was 34.9% (based on DSM-5 criteria) and 35.5% (based on DSM-IV criteria).

The relationship between OUD and duration of therapy is magnified when patients have a history of previous opioid or non-opioid SUD. A cross-sectional cohort study found that provision of LOT (four prescriptions within a 12 month period) to CNCP patients who had a history of severe OUD resulted in increased odds of developing OUD (OR: 56.36, 95% CI: 32.49-97.76).[88]

Patients should be informed that progression from acute to long-term OT is associated with little evidence for sustained analgesic efficacy but a substantial increase in risk for OUD. Providers should discuss this information with patients at initiation of OT and continuously thereafter to ensure that the patient understands the associated risks and benefits of LOT. Fully informed, some patients may desire continuation of OT while others may decline its continued provision.

Research is necessary to more accurately determine how long it takes for OUD to occur and whether the nature of the pain is one of the factors that can influence either of this phenomena.

Recommendation

4. a) We recommend against long-term opioid therapy for pain in patients with untreated substance use disorder. **(Strong against)**
   b) For patients currently on long-term opioid therapy with evidence of untreated substance use disorder, we recommend close monitoring, including engagement in substance use disorder treatment, and discontinuation of opioid therapy for pain with appropriate tapering (see Recommendation 14 and Recommendation 17). **(Strong for)**
   (Reviewed, Amended)

Discussion

Opioids carry a significant risk for OUD, overdose, and death, especially among patients with untreated SUD. The recommendation against LOT for patients with SUD is supported by five large studies (four retrospective case cohort studies and one case cohort study).[59,61,66,86,87] Individually, these studies are of moderate strength; however, the combined weight of their results is strongly supportive of this recommendation. Clinicians should note that this recommendation does not refer to patients whose sole SUD relates to tobacco misuse.

The Edlund et al. (2014) study of 568,640 commercial health plan patients (see Recommendation 2 and 3) found that those diagnosed with CNCP and an alcohol use or non-opioid drug use disorder had higher rates of OUD (OR: 3.22, 95% CI: 1.79-5.80 for patients with pre-index alcohol use disorder compared to no alcohol use disorder; OR: 8.26, 95% CI: 4.74-14.39 for patients with pre-index non-opioid drug use disorders compared to no non-opioid drug use disorders).[86] Moreover, Huffman et al. (2015) found that the presence of a lifetime history of SUD for patients with CNCP was associated with 28 times increased odds of therapeutic opioid addiction compared to patients with CNCP without a lifetime history of SUD (OR: 28.58, 95% CI: 10.86-75.27).[87]

The following three studies concern the serious risks of overdose and death. A study of 206,869 health maintenance organization patients who received opioid prescriptions and who had a diagnosis of an alcohol or drug use disorder were also found to have a significantly higher risk of overdose.[66] The VHA's National Patient Care Database case cohort study of 154,684 patients also found that patients diagnosed with SUD and CNCP had a significantly elevated risk of overdose death (hazard ratio [HR]: 2.53, 95% CI: 1.99-3.22) compared to patients with no SUD diagnosis.[59] The third study used a VHA database to review the outcomes of patients who had been prescribed chronic short-acting or long-acting opioids.[61] This study found that patients who received chronic short-acting or long-acting opioids and who were diagnosed with SUD had an increased risk of suicide attempts compared to those without an SUD diagnosis (OR: 2.42, standard error [SE]: 0.035 for chronic short-acting for patients with drug use disorder; OR: 2.83, SE: 0.057 for chronic long-acting for patients with drug use disorder; OR: 1.99, SE: 0.033 for chronic short-acting for patients with alcohol use disorder; OR: 1.87, SE: 0.056 for chronic long-acting for patients with alcohol use disorder).

Some patients with SUD may disagree with the recommendation to use non-opioid modalities in lieu of LOT to treat their pain. However, the lack of evidence of efficacy of LOT and considerable evidence of significant harms of overdose, death from overdose, and increased risk of suicide outweigh any potential modest benefit of prescribing LOT in this population. See Recommendation 7 for additional information

regarding UDT and risk mitigation. See the VA/DoD SUD CPG for guidance on management of SUD.[7]

Given the increasing use of cannabis among patients with chronic pain and the lack of RCTs comparing outcomes of prescribing LOT versus other therapies for patients with and without cannabis use and cannabis use disorder, future research is needed to optimize care for these patients. Research is also needed to determine which subpopulations of patients with active SUD are at greatest risk of OUD, overdose, and death. Finally, further research is needed on the efficacy of alternative treatments for pain and ways to mitigate risks of opioid-related adverse events in patients with SUD and pain.

Recommendation

5. We recommend against the concurrent use of benzodiazepines and opioids.
   (Strong against | Reviewed, New-added)

   Note: For patients currently on long-term opioid therapy and benzodiazepines, consider tapering one or both when risks exceed benefits and obtaining specialty consultation as appropriate (see Recommendation 14 and the VA/DoD Clinical Practice Guideline for the Management of Substance Use Disorders).

Discussion

Harms may outweigh benefits for the concurrent use of benzodiazepines and LOT. There is moderate quality evidence that concurrent use of benzodiazepines with prescription opioids increases the risk of overdose and overdose death.[66] In a retrospective cohort study, the adjusted odds ratio (AOR) for drug overdose was highest for individuals on LOT for chronic pain (without anxiety or PTSD) who also received concurrent long-term benzodiazepine therapy.[66] In another retrospective study that involved over 200,000 participants (not included in the evidence review), Veterans receiving both opioids and benzodiazepines were at an increased risk of death from drug overdose.[90] Furthermore, there is a lack of evidence in favor of long-term therapy with benzodiazepines and opioids for chronic pain.[91]

There is a large variation in patient preference regarding the concurrent use of benzodiazepines and LOT. This is especially true for patients who are already accustomed to receiving both medications (see Patient Focus Group Methods and Findings). Concurrent benzodiazepine and LOT use is a serious risk factor for unintentional overdose death and should be weighed heavily in the risk-benefit evaluation for tapering versus continuing one or both agents. Once initiated, benzodiazepines can be challenging to discontinue due to symptoms related to benzodiazepine dependence, exacerbations of PTSD, and/or anxiety.[91] Moreover, abrupt discontinuation of benzodiazepines should be avoided, as it can lead to serious adverse effects including seizures and death. Tapering benzodiazepines should be performed with caution and within a team environment when possible (see Recommendation 26 in the VA/DoD SUD CPG).[7] Due to the difficulty of tapering or discontinuing benzodiazepines, particular caution should be used when considering

[7] See the VA/DoD Clinical Practice Guideline for the Management of Substance Use Disorders. Available at: http://www.healthquality.va.gov/guidelines/mh/sud/index.asp

initiating benzodiazepines for Veterans with PTSD who have co-occurring chronic pain. The VA/DoD PTSD CPG[8] recommends against benzodiazepines for the prevention of PTSD and cautions against their use in treatment of PTSD. Benzodiazepines to treat acute anxiety symptoms after trauma are associated with a higher incidence of PTSD symptoms. For treatment of PTSD, there is evidence of lack of efficacy from small clinical trials and evidence of harm from observational studies of benzodiazepines for PTSD. Although anxiety may initially improve with benzodiazepines, the improvement is short-lived and may result in tolerance to increasing doses and eventual failure of the treatment. Even gradual benzodiazepine taper may result in exacerbation of severe PTSD symptoms. Concomitant use of benzodiazepines is considered a contraindication to initiation of OT.

In addition to benzodiazepines, the addition of other psychoactive medications to LOT must be made with caution. While the evidence for harm associated with the combination of opioids and Z-drugs (e.g., zolpidem, eszopiclone) is not as strong as the evidence for harm associated with the combination of opioids and benzodiazepines, we suggest not prescribing Z-drugs to patients who are on LOT, as moderate quality evidence demonstrates that the combination of zolpidem and opioids increases the AOR of overdose.[66] The evidence reviewed also identifies potential adverse outcomes (e.g., risk of overdose) with the combined use of antidepressants and opioids in patients who do not have depression.[66] This particular study did not differentiate between classes of antidepressants, limiting the ability of the Work Group to recommend for or against prescribing opioids and a specific class of antidepressants. As such, there is no recommendation in this guideline with respect to using specific classes of antidepressants and LOT.

Recommendation

6. a) We recommend against long-term opioid therapy for patients less than 30 years of age secondary to higher risk of opioid use disorder and overdose. **(Strong against)**
   b) For patients less than 30 years of age currently on long-term opioid therapy, we recommend close monitoring and consideration for tapering when risks exceed benefits (see Recommendation 14 and Recommendation 17). **(Strong for)**
   (Reviewed, New-replaced)

Discussion

All patients who take opioids chronically are at risk for OUD and overdose, but especially those who are younger than 30 years of age. Seven studies were identified that examined age as a predictor of OUD, respiratory/CNS depression, and/or overdose. Four of the seven studies were rated as fair quality evidence,[59,86,88,92] while three were rated as poor quality evidence.[58,62,87] Six of the seven studies demonstrated that age was inversely associated with the risk of OUD and overdose.[59,62,86-88,92] One

[8] See the VA/DoD Clinical Practice Guideline for the Management of Posttraumatic Stress Disorder and Acute Stress Disorder. Available at: http://www.healthquality.va.gov/guidelines/MH/ptsd/

of the three low quality studies showed that older subjects had a higher HR of overdose.[58] The Work Group's overall confidence in the quality of the evidence was moderate.

Similar to other risk factors, age <30 years should be weighed heavily in the risk-benefit determination for initiating LOT. Age <30 years is not an absolute contraindication to LOT. There may be some situations where the benefits of LOT clearly outweigh the risks of OUD and overdose. Hospitalized patients recovering from battlefield injuries, for example, are known to have less chronic pain, depression, and PTSD when their pain is aggressively managed starting soon after injury.[93] In those cases, LOT may be appropriate only if risk mitigation strategies are employed and patients are titrated off LOT as soon as it is appropriate (see Recommendations 14 and 15).

The added risk that younger patients using opioids face for OUD and overdose is great. Edlund et al. (2014) found that, compared to patients ≥65 years old, patients 18-30 years old carried 11 times the odds of OUD and overdose. Patients 31-40 years old carried 5 times the odds of OUD and overdose compared to those ≥65 years old.[86] Bohnert et al. (2011) found that, compared to subjects 18-29 years old, patients 30-39 years old had roughly half the risk of developing OUD or overdose (HR: 0.56, 95% CI: 0.27-1.17). Compared to the subjects 18-29 years old, patients ≥70 years old had a far less risk (nearly 1/17) of developing OUD or overdose (HR: 0.06, 95% CI: 0.02, 0.18).[59]

Younger patients are also at a higher risk of opioid misuse (as suggested by a UDT indicating high-risk medication-related behavior). Turner et al. (2014) showed that patients in the 45-64 year age group were significantly less likely to have an aberrant UDT (detection of a non-prescribed opioid, non-prescribed benzodiazepine, illicit drug, or tetrahydrocannabinol [THC]) in comparison to patients in the 20-44 age group.[94] Patients in the 45-64 and ≥65 age groups were significantly less likely than 20-44 year olds to have non-detection of a prescribed opioid as well (indicating possible diversion).[94]

An age of 30 years was chosen based on how age was categorized in the six studies that showed an inverse relationship between age and OUD or overdose. One of those six studies found that patients with OUD were younger than patients without OUD, but did not find a statistically significant relationship.[87] Two of those six studies examined age as a continuous predictor, and neither reported a specific age where the risk of OUD or overdose changed markedly.[62,92] One study examined age as a dichotomous (<65 and ≥65) predictor.[88] In the two remaining studies, the highest risk included ages ranging from 18 to 30 years.[59,86] As such, the Work Group chose 30 years of age as a clinically reasonable threshold.

Some may interpret the recommendation to limit opioid use by age as arbitrary and potentially discriminatory when taken out of context; however, there is good neurophysiologic rationale explaining the relationship between age and OUD and overdose. Studies in other areas (e.g., use of different substances) indicate that developing brains (age <30 years) are at increased risk of abnormalities and addiction when exposed to substance use early in life.[95-98]

Toward augmenting this evidence base, we recommend that future observational research examine age as a continuous predictor of adverse outcomes. Additionally, we recommend that future trials examine which risk mitigation strategies can reduce the additional risk of OUD and overdose in younger patients on LOT. Lastly, a deeper understanding of the mechanisms for addiction to opioids in young brains is needed.

B. Risk Mitigation

Recommendation

7. We recommend implementing risk mitigation strategies upon initiation of long-term opioid therapy, starting with an informed consent conversation covering the risks and benefits of opioid therapy as well as alternative therapies. The strategies and their frequency should be commensurate with risk factors and include:
   - Ongoing, random urine drug testing (including appropriate confirmatory testing)
   - Checking state prescription drug monitoring programs
   - Monitoring for overdose potential and suicidality
   - Providing overdose education
   - Prescribing of naloxone rescue and accompanying education

   (Strong for | Reviewed, New-replaced)

Discussion

Risk mitigation for LOT should begin before the opioids are prescribed, through an informed consent discussion, reviewing the patient's history, checking state PDMPs, or instructing patients about using drug take back programs to dispose of unused medication. It should also occur concurrently with the therapy (e.g., ongoing UDT, OEND) and in response to adverse events (e.g., needle exchange programs for those who develop an intravenous drug use disorder). The 2010 OT CPG recommended use of an opioid pain care agreement, monitoring for appropriate opioid use, and, with patients' consent, obtaining a UDT. A literature search was conducted dating back to the original 2010 recommendation to identify studies comparing the effectiveness of different risk mitigation strategies for patients on or being considered for LOT. One identified study was a systematic review of 11 studies looking at opioid treatment agreements (OTAs) and UDT strategies utilizing opioid misuse risk reduction as the main outcome measure.[99] The study revealed weak evidence to support the use of OTAs and UDT. A second study, a retrospective database study, demonstrated decreased risk of suicide attempts in various cohorts with frequent UDT, regular follow-up (including follow-up within four weeks for patients with new opioid prescription), and rehabilitative services are offered.[61] The confidence in the quality of the evidence was moderate for the outcome of attempted suicide risk. The third study was a retrospective cohort study that looked at the intervention of a clinical pharmacist guidance team versus control.[100] Outcome measures included adverse events, pain management, and quality of life. Details of the actual intervention were vague and did not necessarily include OTAs or UDT. Thus, the confidence in the quality of the evidence was very low.

The confidence in the quality of the evidence was moderate for UDT and frequent follow-up and was low for OTAs. The frequency of follow-up and monitoring should be based on patient level of risk as determined by an individual risk assessment.

There may be some variation in patient values and preferences. Certain patients may appreciate the use of risk mitigation strategies and others may not. Participants in the patient focus group expressed an understanding of why various risk mitigation strategies were used (see Patient Focus Group Methods and Findings).

Implementing more extensive risk mitigation strategies entails an investment of resources. Primary care providers may require more time with patients to allow for shared decision making and treatment

planning. More frequent follow-up of patients on LOT can affect access to care for all empaneled patients. VHA providers must also follow VHA policy regarding education and signature informed consent when providing LOT for patients with non-cancer pain.[101]

Written Informed Consent and Opioid Treatment Agreements

There is a paradigm shift occurring in approaches to ensuring and documenting patient and provider understanding and expectations regarding the risks and benefits of LOT. The 2010 OT CPG reflected prior practice of using opioid treatment (or pain care) agreements. OTAs have been described as coercive rather than therapeutic, lack respect for individual autonomy, can be a barrier to pain care, and may be harmful to the patient-provider relationship.[102-105]

Given the recognized risks of opioid therapy, an optimal approach to care should include a robust, signature informed consent process that is patient-centered and provides patients with information about known benefits and harms of OT and treatment alternatives. In 2014, VA established a requirement for signature informed consent, consistent with VA policy for other treatments or procedures with a significant risk of complications or morbidity. See Appendix A, *Taking Opioids Responsibly for Your Safety and the Safety of Others: Patient Information Guide on Long-term Opioid Therapy for Chronic Pain* (found at http://www.healthquality.va.gov/guidelines/Pain/cot/OpiodTheraphyforChronicPainPatientTool20May2013print.pdf), and 38 C.F.R. §17.32 (2012).

Patients may decline offered treatments (e.g., OT) and may also decline risk mitigation strategies (e.g., UDT, pill counts) that are recommended in the course of clinical care. However, providers should discuss this decision with the patient, including the likelihood that their decision may result in the risks of LOT outweighing its potential benefits. This would require a consideration of patient's safety, and a clinical decision may be made not to initiate OT or to discontinue ongoing OT through tapering (see Recommendation 14 and Recommendation 17).

State Prescription Drug Monitoring Programs

State database queries for detection of multi-sourcing of controlled substances are used throughout the country. Data comparing states with an implemented state database program to states without one showed 1.55 fewer deaths per 100,000 people.[106] The CDC currently recommends at least quarterly checks of the state database system.[33]

Urine Drug Testing and Confirmatory Testing

As substance misuse in patients on LOT is more than 30% in some series,[107] UDT and confirmatory testing is used as an additional method of examining for patient substance misuse and adherence to the prescribed regimen. UDTs, used in the appropriate way, help to address safety, fairness, and trust with OT.

Availability of accurate and timely confirmatory testing (e.g., gas chromatography-mass spectrometry [GCMS]) is critical due to the false positive and negative rates associated with UDTs.[53] Interpretation of a UDT and confirmatory results requires education and knowledge of the local procedures and clinical scenario. Local education and access to expert interpretation is necessary.

UDT results are helpful and can help identify active SUD or possible diversion. Accordingly, clinicians should

obtain UDT prior to initiating or continuing LOT and periodically thereafter. When a patient is referred for SUD treatment or is engaged in on-going treatment there should be close communication between the SUD and pain management providers. The ideal approach is an interdisciplinary format (see Recommendation 16).

For more information, see Appendix B on UDT and confirmatory testing.

Prescribing of Naloxone Rescue and Accompanying Education

Naloxone administration has been identified as a life saving measure following opioid overdose. A systematic review of 22 observational studies provided moderate quality evidence that take home naloxone programs are effective in improving overdose survival and decreasing mortality, with a low rate of adverse events.[108] One meta-analysis of nine studies determined that take home naloxone kits were used approximately nine times within the first three months of follow-up for every 100 individuals trained.[109] Further, studies have shown that naloxone administration has been efficacious whether given by medical personnel or lay people, with more than 26,000 reversals documented by the CDC from 1996-2014.[110,111] In addition, prescription of naloxone rescue and accompanying education has also been found to reduce opioid-related emergency department visits.[112] Distribution of naloxone for reversal is supported by SAMHSA, the American Medical Association (AMA), and other medical societies, and is facilitated through the VA via Pharmacy Benefits Management. Clinical efficacy has been established for its use on short-acting opioids, but not for its use on long-acting opioids such as methadone or exceptionally potent opioids.[108]

Synthetic opioids such as fentanyl analogs, potent opioid receptor agonists, are responsible for a recent rise in death rates. Fentanyl analogs that may be used to create counterfeit opioid analgesic pills can cause a toxidrome characterized by significant CNS and profound respiratory depression requiring multiple naloxone doses for reversal.[113]

Patients at High Risk for Opioid Use Disorder

Those patients receiving opioid analgesics who do not meet DSM-5 criteria for OUD may benefit from an alternative management strategy: close follow-up and CBT. Jamison et al. (2010) randomized patients at high-risk for OUD (as measured by standard rating scales) to receive either standard pain management or close follow-up with CBT for pain.[114] Both of these groups were compared to a low-risk, chronic pain control group receiving standard management. The authors report that, compared to a matched high-risk group receiving standard care, patients receiving additional monitoring and CBT exhibited significantly reduced illicit substance use over six months (percentage of patients with positive drug misuse index scores: 73.7% versus 26.3% versus 25.0%; $p<0.01$). At six months, there was no difference between the high-risk group receiving close follow-up and the low-risk group receiving standard therapy. Authors also reported that pain perception was less in the high-risk group receiving additional monitoring and behavior therapy; however, analysis of activity interference reporting reflected no significant difference between study groups.

Other Risk Mitigation Strategies

Take Back Programs

Returning unused opioid medications has been explored as a strategy to reduce the amount of opioids in the community, as it has been estimated that 70% of opioid prescriptions are left unused.[115] Accordingly, the National Drug Control Strategy advocates take back programs as an effective tool.[24] For example, in a 2013 medication take back event in a Michigan community, 3,633 containers containing 345 different prescription medications were collected in four hours. The top five most common medications collected were pain relievers.[116] System-wide efficacy of a nationwide program is unknown.[117]

Community-based Needle Exchange Programs or Syringe Service Programs

Nearly 80% of new users of injectable opioids had previously used prescription oral opioid pain medication.[118,119] Illicit use of injectable opioids is accompanied by an increased rate of human immunodeficiency virus (HIV) and hepatitis infection. Community-based needle exchange programs have been shown to be an effective risk mitigation strategy for reducing high-risk behaviors (e.g., sharing needles) and infectious disease transmission among injection drug users.[120] For those patients who develop OUD and progress to intravenous drug use, the first recommendation should be for medication-assisted treatment (MAT) for OUD (see Recommendation 17). For patients who decline MAT for OUD, clinicians should consider educating the patient regarding sterile injection techniques and community-based needle exchange programs, if programs are available. The 2015 outbreak of HIV/hepatitis in rural Indiana and subsequent successful implementation of a needle exchange program is an example of the threat to rural communities from non-prescription opioid use and the potential benefits of needle exchange programs for use as a risk mitigation strategy.[121,122]

Recommendation

8. We recommend assessing suicide risk when considering initiating or continuing long-term opioid therapy and intervening when necessary.
   (Strong for | Reviewed, Amended)

Discussion

Opioid medications are potentially lethal and an assessment of current suicide risk should be made at every phase of treatment. The VA/DoD Suicide CPG[9] recommends restricting the availability of lethal means for patients considered to be at intermediate or high acute risk of suicide (determined by presence and severity of suicidal ideation, level of intention to act, existence of risk factors, limited or absent protective factors, etc.). Accordingly, suicidality is considered to be an important risk factor for OT (see Risk Factors for Adverse Outcomes of Opioid Therapy).

[9] See the VA/DoD Clinical Practice Guideline for Assessment and Management of Patients at Risk of Suicide. Available at: http://www.healthquality.va.gov/guidelines/MH/srb/

A number of studies suggest certain chronic pain conditions represent an independent risk factor for suicide.[123-130] A recent large retrospective cohort study also suggests an association with prescribed opioid dose and suicide risk among Veterans receiving OT for CNCP.[131] Suicide risk is not static, and many factors influence an individual's risk of suicide at any given point in time, as noted in the VA/DoD Suicide CPG.[10] Thus, ongoing assessment of suicide risk is important whether one is initiating, maintaining, or terminating LOT.

There is moderate quality evidence that intensification of monitoring helps mitigate the risk of suicide among patients on LOT. Im et al. (2015) found moderate quality evidence that, at the facility level, patients on LOT within facilities ordering more drug screens than the comparison group were associated with decreased risk of suicide attempt (chronic short-acting opioid group: OR: 0.2, 95% CI: 0.1-0.3; chronic long-acting opioid group: OR: 0.3, 95% CI: 0.2-0.6). In addition, patients on long-acting opioids within the facilities providing more follow-up after new prescriptions were associated with decreased risk of suicide attempt (OR: 0.2, 95% CI: 0.0-0.7).[61]

Some patients on LOT who suffer from chronic pain and co-occurring OUD, depression, and/or personality disorders may threaten suicide when providers recommend discontinuation of opioids. However, continuing LOT to "prevent suicide" in someone with chronic pain is not recommended as an appropriate response if suicide risk is high or increases. In such cases, it is essential to involve behavioral health to assess, monitor, and treat a patient who becomes destabilized as a result of a medically appropriate decision to taper or cease LOT.

Further research is needed to identify strategies for safely managing patients at elevated risk of suicide who demand opioid medications or become further destabilized during tapering.

Recommendation

9. We recommend evaluating benefits of continued opioid therapy and risk for opioid-related adverse events at least every three months.
   (Strong for | Reviewed, New-replaced)

Discussion

Prior to initiating OT, an individualized assessment of potential opioid-related harms relative to realistic treatment goals must be completed. After initiating OT, frequent visits contribute to the appropriate use and adjustment of the planned therapy.

The Work Group recommends follow-up at least every three months or more frequently (see Recommendation 7 and Recommendation 11) due to the balance of benefits and harms associated with this recommendation. Although the 2010 OT CPG recommended follow-up every six months, this

[10] See the VA/DoD Clinical Practice Guideline for Assessment and Management of Patients at Risk of Suicide. Available at: http://www.healthquality.va.gov/guidelines/MH/srb/

recommended interval for follow-up and reassessment has not been sufficient to reduce the potential harm associated with LOT or adequately implement comprehensive, biopsychosocial pain care. More frequent follow-up is needed in order to increase the impact of risk mitigation strategies and enhance the delivery of comprehensive, biopsychosocial pain care. Frequency of visits should thereafter be based on risk stratification. Similarly, the CDC guideline for OT recommends re-evaluating harms versus benefits within one to four weeks of starting OT or at any dose change, and at least every three months or more frequently if needed.[132]

At follow-up visits, a clinician should re-examine the rationale for continuing the patient on OT. Clinicians should take into account changes in co-occurring conditions, diagnoses/medications, and functional status when conducting the risk/benefit analysis for LOT. Alcohol use, pregnancy, nursing of infants, and lab abnormalities may change the risk/benefit calculus for LOT. Ongoing OT prescribing practice may include pharmacy review, informed consent, UDTs, and checking state PDMPs. A clinician should also be mindful of signs of diversion during follow-up (see Risk Factors for Adverse Outcomes of Opioid Therapy). The longer the patient is on opioids, the greater the potential for change in patient status and development of opioid-related harms.

C. Type, Dose, Duration, Follow-up, and Taper of Opioids

Recommendations

10. If prescribing opioids, we recommend prescribing the lowest dose of opioids as indicated by patient-specific risks and benefits.
    (Strong for | Reviewed, New-replaced)

    Note: There is no absolutely safe dose of opioids.

11. As opioid dosage and risk increase, we recommend more frequent monitoring for adverse events including opioid use disorder and overdose.
    - Risks for opioid use disorder start at any dose and increase in a dose dependent manner.
    - Risks for overdose and death significantly increase at a range of 20-50 mg morphine equivalent daily dose.

    (Strong for | Reviewed, New- replaced)

12. We recommend against opioid doses over 90 mg morphine equivalent daily dose for treating chronic pain.
    (Strong against | Reviewed, New-replaced)

    Note: For patients who are currently prescribed doses over 90 mg morphine equivalent daily dose, evaluate for tapering to reduced dose or to discontinuation (see Recommendations 14 and 15).

Discussion

There is moderate quality evidence from retrospective cohort and retrospective case control studies indicating that risk of prescription opioid overdose and overdose death exists even at low opioid dosage levels and increases with increasing doses. Significant risk (approximately 1.5 times) exists at a daily dosage range of 20 to <50 mg MEDD and further increases (approximately 2.6 times) at a range of 50 to <100 mg

MEDD compared to risk at <20 mg MEDD. Risk continues to increase at higher dosage ranges (≥100 mg MEDD) (Table 2).[58,59,66,133]

Table 2. Risks of Prescription Opioid Overdose and Overdose Death at Selected Morphine Equivalent Daily Dose Intervals [58,59,66,133]

Study	Expression of risk	MEDD (mg)				
		0	1 to 19	20 to <50	50 to <100	≥100
Turner and Liang (2015)[1] [66]	AOR (95% CI)	1	0.80 (0.50-1.27)	1.54 (1.23-1.94)	2.08 (1.61-2.69)	4.34 (3.37-5.57)
Zedler et al. (2014)[1,2,3] [58]	OR (95% CI)	-	1	1.5 (1.1-1.9)	2.2 (1.5-3.2)	4.1 (2.6-6.5)
Dunn et al. (2010)[1] [133]	HR (95% CI)	0.19 (0.05-0.68)	1	1.19 (0.40-3.60)	3.11 (1.01-9.51)	11.18 (4.80-26.03)
Bohnert et al. (2011)[1,3] [59]	HR (95% CI)	-	1	1.88 (1.33-2.67)	4.63 (3.18-6.74)	7.18 (4.85-10.65)
Bohnert et al. (2011)[2,3] [59]	HR (95% CI)	-	1	1.74 (0.69-4.35)	6.01 (2.29-15.78)	11.99 (4.42-32.56)

[1]Chronic non-cancer pain; [2]Chronic cancer pain; [3]Study conducted in U.S. Veterans

Abbreviations: AOR: adjusted odds ratio; 95% CI: 95% confidence interval; HR: hazard ratio; MEDD: morphine equivalent daily dose; OR: odds ratio

In a nested case-control study of U.S. Veterans (not included in our evidence review as it was published after the end of the search date range), Bohnert et al. (2016) examined the association between prescribed opioid dose as a continuous measure (in 10 mg MEDD increments) and overdose.[134] Prescribed opioid dosage was a moderately good predictor of overdose death, but the study did not reveal a specific dosage cut point or threshold above which risk of overdose increased dramatically. Lower prescribed opioid dosages were associated with reduced risk for overdose, but risk was not completely eliminated at lower doses; approximately 40% of overdoses were observed in patients who were prescribed <50 mg MEDD.

In a prospective cohort study (not included in the evidence review as it did not include information on acute versus chronic pain in the patient population), Dasgupta et al. (2015) compared residents of North Carolina who had received an opioid prescription in the last year to residents who had not. The study examined the outcome of population-based rates of opioid overdose mortality by opioid dose, without use of a presupposed threshold (Table 3).[135] There was no safe dose of opioid. Among the over nine million individuals followed for one year, 629 died from opioid overdose. Of these 629 individuals, 151 had no record of having been dispensed an opioid. It is possible these opioids were obtained through illicit channels or social sharing/diversion. Of the 478 patients who died from an opioid overdose who were prescribed opioids, 235 (49%) had been prescribed <80 mg MEDD. Overdose incidence rate ratios (IRRs) doubled each time the MEDD ranges increase from 60.0-79.9 mg to 80.0-99.9 mg (IRR 2.9 to 6.2), then to 120-139.9 mg (IRR 14.1), 160-179.9 mg (IRR 29.5), and 350-399.9 mg (IRR 63.2).

Table 3. Incidence Rate Ratios for Opioid Overdose Deaths, by Average Milligrams Morphine Equivalent Daily Dose[135]

MEDD (mg)	Deaths	Person-Years	Sample Size	IRR	95% CI
Unexposed	151	3,554,850	7,377,860	0.57	0.44-0.73
>0 - 39.9	98	1,305,835	1,305,969	1	
40 - 59.9	90	457,227	457,322	2.6	2.0-3.5
60 - 79.9	47	213,816	213,868	2.9	2.1-4.1
80 - 99.9	34	72,448	72,483	6.2	4.2-9.2
100 - 119.9	23	45,536	45,559	6.7	4.3-10.6
120 - 139.9	22	20,699	20,721	14.1	8.9-22.5
140 - 159.9	14	14,586	14,599	12.8	7.3-22.4
160 - 179.9	15	6,769	6,784	29.5	17.1-50.7
180 – 199.9	11	9,604	9,615	15.2	8.2-28.4
200 – 249.9	24	11,653	11,678	27.4	17.5-42.8
250 – 299.9	20	7,406	7,425	35.9	22.2-58.0
300 – 349.9	17	4,495	4,512	50.2	30.0-84.0
350 – 399.9	17	3,563	3,580	63.2	37.8-105.7
400 – 499.9	14	3,527	3,541	52.7	30.1-92.2
500 – 5000	32	4,684	4,718	90.4	60.7-134.6
Total	**629**	**5,736,696**	**9,560,234**	--	--

Abbreviations: 95% CI: 95% confidence interval, IRR: incidence rate ratios; MEDD: morphine equivalent daily dose; mg: milligram(s)

Achieving an improved understanding of the factors contributing to prescription opioid-related overdose is an essential step toward addressing this epidemic problem. Although it is widely accepted that progressively higher doses of prescribed opioids result in correspondingly higher risks of opioid overdose, patients using any dose of opioids can still experience life-threatening respiratory or CNS depression, especially when opioid-naïve. This risk begins to increase with MEDD as low as 20-50 mg. Risk is further increased when certain concomitant demographic factors, co-occurring medical or psychiatric conditions, or interacting medications or substances exist.

Recognizing the lack of evidence of long-term benefit associated with LOT used alone and the risks of harms with use of opioids without risk mitigation, dosing determinations should be individualized based upon patient characteristics and preferences, with the goal of using the lowest dose of opioids for the shortest period of time to achieve well-defined functional treatment goals. Understandably, there will be greater mortality, co-occurring medical conditions, and other adverse events in patients who require higher doses of opioids, even in those who benefit from such therapy. When closer follow-up is needed, healthcare resources and patient adherence should be considered.

Subgroups at higher risk

Risk of prescription opioid overdose is elevated across MEDD dosage levels in patients with co-occurring depression (moderate quality evidence).[66,133] Following an elevated baseline adjusted risk ratio (ARR) of 3.96, depressed patients taking 1-19 mg, 20 to <50 mg, 50 to <100 mg, and ≥100 mg MEDD had

respective odds of overdose of 4.75, 5.47, 6.44, and 7.06, compared to those taking an opioid at the same dosage level without a diagnosis of depression.[66]

Similarly, a history of or active SUD increases risk for serious prescription opioid-related toxicity or overdose across opioid dosages (moderate quality evidence).[58,87,133] A retrospective cohort review of patients with CNCP receiving LOT at least five days per week for 90 days determined that those with a history of non-opioid SUD had 28 times the odds of developing OUD.[87] Each 50 mg increase in MEDD nearly doubled the odds while each 100 mg MEDD increase tripled the risk for OUD. Concurrent prescribing of sedative-hypnotics and benzodiazepines increases risk of fatal or non-fatal opioid overdose 2-10 fold across opioid dose ranges.[66,133,135]

There is moderate quality evidence to support that opioids taken PRN (as needed) for chronic cancer pain versus regularly scheduled doses, or simultaneous PRN plus regularly scheduled, places patients at elevated risk for opioid overdose (HR: 2.75, 95% CI: 1.31-5.78 for as needed; HR: 1.00 for regularly scheduled; HR: 1.84, 95% CI: 0.83-4.05 for simultaneous PRN plus regularly scheduled).[59]

In patients receiving LOT, moderate quality evidence indicated that men are 50% more likely (HR: 1.44, 95% CI: 1.21-1.70) to escalate to high-dose opioids (defined as >200 mg MEDD) and twice as likely to experience an opioid-related death (adjusted HR: 2.04, 95% CI: 1.18-3.53) compared to women.[136] Risk of opioid overdose morbidity or mortality is also increased in non-Hispanic white versus non-Hispanic black patients (moderate quality evidence).[59,136]

Future Research

Future research is needed to better determine the impact of systematic reductions in MEDD in terms of pain relief, specific pain and medical conditions, overdose morbidity and mortality as well as potential adverse outcomes (e.g., the incidence of associated OUD, infectious diseases related to intravenous drug use disorder, and drug-related crime and diversion) and to determine whether/which conditions may be appropriately treated with LOT. Research is also needed to determine how frequency of monitoring should be impacted by dose.

Recommendation

13. We recommend against prescribing long-acting opioids for acute pain, as an as-needed medication, or on initiation of long-term opioid therapy.
    (Strong against| Reviewed, New- replaced)

Discussion

Long-acting opioids, as further discussed below, should not be used for treatment of acute pain, on an as-needed basis, or during initiation of LOT (see Short-acting versus Long-acting Opioids). In general, however, no single opioid or opioid formulation is preferred over the others. However, individuals may have a better response, degree of safety, or tolerability depending on their individual characteristics and preferences. Additional information for use when deciding on appropriate pharmacological treatment of pain for a specific patient can be found in Appendix D.

There was insufficient evidence to recommend for or against any specific opioid or opioid formulation, specifically the following:

- Short-acting versus long-acting opioids (for LOT for chronic pain)
- Route of administration/delivery among alternatives such as transdermal, buccal, sublingual, or pumps
- Abuse deterrent formulations of opioids compared to non-abuse deterrent formulations
- Tramadol and other dual-mechanism opioids
- Buprenorphine for pain (compared to other opioids)
- Methadone (with QT monitoring)

Short-acting versus Long-acting Opioids

Avoid use of long-acting agents for acute pain (with exception of oxycodone/acetaminophen extended-release [ER] tablets), on an as-needed basis, or for initiation of OT.[10,137-139] There is very low quality evidence to recommend for or against short-acting versus long-acting opioids for maintenance of OT.

There were two RCTs included in the evidence review that looked at safety and efficacy. One RCT comparing long-acting to short-acting dihydrocodeine found no statistically or clinically significant differences in stability of pain intensity between the two groups, as well as no difference in adverse events. Although study results may be inconclusive due to poor study design, the authors state that they do not support the use of long-acting agents for chronic non-malignant pain.[140]

A second non-inferiority RCT compared once-daily hydromorphone ER to twice-daily oxycodone controlled-release in patients with moderate-to-severe cancer pain. The primary efficacy endpoint was patient assessment of "Brief Pain Inventory (BPI) worst pain in the past 24 hr." Results demonstrated similar improvements in BPI and that the once-daily hydromorphone formulation was non-inferior to the twice-daily oxycodone formulation. Treatment-emergent adverse events were comparable between the groups as well.[141] The efficacy of long-acting opioids used once-daily is non-inferior to twice-daily use. There was a lack of statistical analysis of the outcomes and a lack of statistical power in both studies, and a small sample size in one study.

There is concern for additional overdose risk associated with long-acting versus short-acting opioids. A study (not included in the evidence review due to its design) suggests increased risk for non-fatal overdose in VA patients with initiation of a long-acting opioid compared with immediate-release opioids.[137] Also, recent research demonstrates that patients with CNCP on long-acting OT have a significantly increased risk of all-cause mortality compared to patients with CNCP who are taking an analgesic anticonvulsants or a low-dose antidepressant.[10]

Route of Administration/Delivery

The systematic evidence review for this CPG did not find any studies that compared alternative delivery systems (e.g., fentanyl transdermal, fentanyl buccal) to other delivery systems (e.g., oral, intravenous) (information on transdermal and sublingual buprenorphine is included in the following section on Buprenorphine for Pain). The concomitant use of oral and transdermal opioids or oral and intrathecal

pumps should be approached with extreme caution and warrants specialty consultation. Discussions of intrathecal pumps are beyond the scope of this guideline.

Although some patients may prefer either transdermal or buccal opioid delivery for opioids, there is significant potential for harm from OT with these delivery mechanisms, with no evidence of benefit over traditional opioid delivery systems in patients with chronic pain. Clinicians need to be especially aware of the risks associated with a fentanyl transdermal delivery system (or patch) (Appendix D) including its:

- Unique pharmacokinetic profile
- Continuous delivery, even after the patch is removed due to depot effect
- Increased rate of delivery
- Unpredictable variation in rate of delivery
    - Due to alterations in temperature due to external heat, skin integrity, and amount of adipose tissue
    - Among patients with fever, skin damage, or cachexia

Given the potential serious risks with starting fentanyl and challenges with tapering, clinicians intent on prescribing transdermal fentanyl for chronic pain are encouraged to consult with other clinicians (e.g., pain specialists, pharmacists) and to be familiar with the unique properties of fentanyl. Specific safety precautions that all clinicians should be aware of regarding transdermal fentanyl include:

- Transdermal fentanyl should not be used in opioid-naïve patients
- Patients need to be informed that:
    - Heat (e.g., sun exposure, heating pad, febrile condition) can increase the rate and quantity of absorption
    - Proper application includes: being sure to take old patch off; never applying damaged patch or a patch to non-intact skin; proper disposal to avoid exposure to children and pets, and precautions taken against possible diversion of remaining drug in used patch
- Adjusted dose (i.e., decreased patch size) should be used in patients with renal or hepatic insufficiency and considered in elderly patients and those with febrile illness

Abuse Deterrent Formulations of Opioids

The aim of most abuse deterrent formulations is to present a physical barrier to prevent chewing, crushing, cutting, grating, or grinding of the dosage form, or present a chemical barrier, such as a gelling agent, that will resist extraction of the opioid with use of a common solvent. Alternatively, an opioid antagonist (naloxone or naltrexone) can be added to interfere with, reduce, or defeat the euphoria associated with abuse of an agent intended for oral use when taken nasally or parenterally.[142] While these properties deter abuse they do not fully prevent abuse; no opioid formulation prevents consumption of a large number of intact capsules or tablets which continues to be the most common method of abuse.

We do not recommend for or against abuse deterrent formulations for LOT. Our searches identified two RCTs in which the benefits of co-prescribing of naloxone with opioids were examined.[143,144] However,

both RCTs were rated as low to very low quality with short-term follow-up. One open-label RCT enrolling 453 patients with chronic low back pain considered the safety and tolerability of an abuse deterrent formulation of oxycodone/naloxone relative to oxycodone or morphine at 12-week follow-up.[143] Another RCT considered the safety and efficacy of oxycodone/naloxone prolonged-release relative to oxycodone prolonged-release in 184 patients with moderate-to-severe chronic cancer pain at four-week follow-up.[144] An observational study (not included in the evidence review) suggested that the introduction of abuse deterrent opioid formulations did not help reduce abuse of opioids as a class and that patients may switch from one opioid to another based on the availability or the lack of availability of abuse deterrent formulations.[145]

Future research is needed to ascertain whether abuse deterrent formulations actually reduce OUD when used for chronic pain, and whether said formulations differ across clinical outcomes such as pain, function, and adverse events.

Dual-Mechanism Opioids

Dual-mechanism opioids include formulations of an opioid medication with a selective serotonin reuptake inhibitor (SSRI) or a serotonin-norepinephrine reuptake inhibitor (SNRI). Two common examples are tramadol and tapentadol. While both are dual-mechanism opioids, they differ in their affinity for the mu opioid receptor, resulting in partial versus full agonist effects, and as such are discussed separately.

Tramadol

There is low quality evidence that tramadol may be more effective than placebo for pain relief. In one short-term study, compared to placebo, tramadol was more effective for pain.[146] There is no long-term evidence of the comparative efficacy of tramadol versus another opioid or a non-opioid comparison such as non-steroidal anti-inflammatory drugs (NSAIDs) or acetaminophen. Due to tramadol's partial mu agonist activity and demonstrated safety profile when used in conjunction with acetaminophen in elderly patients, it may be a preferred agent in that patient group.[147,148]

Tapentadol

In long-term studies, compared to placebo, low quality evidence indicates that tapentadol is more effective for pain-related primary and secondary outcomes, but results were mixed for several different self-reported quality of life measures in these studies.[149-151] Compared to oxycodone, moderate quality evidence suggests that tapentadol might be more effective for pain relief. Low quality evidence suggests there is no difference in serious adverse events. Moderate quality evidence suggests tapentadol might be superior for avoiding non-serious adverse events or discontinuation of treatment due to adverse events; however, the clinical implications of these findings are unclear.[149]

Safety and Risk Mitigation

All recommendations in this CPG apply to dual-mechanism opioid products, including the recommendations regarding safety measures and risk mitigation strategies (e.g., to monitor for suicidality, accidental overdose, and OUD).

Dual-mechanism opioid medications have additional considerations as a result of their dual action. They include a lowering of seizure threshold in susceptible patients and the risk of serotonin syndrome.

Evidence related to safety of dual-mechanism opioids versus placebo was reviewed. No evidence on the safety of tramadol met our inclusion criteria, and no new evidence was reviewed. Tramadol may be considered lower-risk than tapentadol due to its mechanism of action and existing safety profile as noted above. Evidence on the safety of tapentadol was reviewed for this guideline update. In long-term studies, there is low quality evidence that, when compared to placebo, patients experience more adverse events when taking tapentadol. Some severe adverse events experienced by a small portion of patients receiving tapentadol included chest pain,[150,151] coronary artery disease,[151] and severe upper abdominal pain possibly related to the study drug.[150] There was one death due to myocardial ischemia but this was not likely related to tapentadol. In one study comparing tapentadol versus placebo, minor adverse events observed in patients treated with tapentadol included nausea and vomiting in 21.1% and 12.7% of patients, respectively.[151] In short-term studies, there is overall low to very low quality evidence that, when compared to placebo, patients receiving tapentadol experience more adverse events (e.g., vomiting, tiredness, dry mouth, dizziness, sweating, constipation, nausea) and drop out of treatment more often than the placebo groups.[146,152-154]

Buprenorphine for Pain

There is insufficient evidence to recommend buprenorphine over other opioids for the treatment of chronic pain. Transdermal buprenorphine was found to be efficacious and well-tolerated for the short-term treatment of chronic, moderate-to-severe low back pain.[155] In patients with chronic, moderate-to-severe osteoarthritis (OA) pain of the hip and/or knee, short-term use of seven-day low-dose buprenorphine patches were an effective and well-tolerated analgesic.[156] Furthermore, during a 28-day assessment period, seven-day low-dose transdermal buprenorphine patches were as effective as sublingual (SL) buprenorphine, with a better tolerability profile.[157] In terms of dosing, transdermal buprenorphine provides effective analgesia with an acceptable tolerability profile when initiated at 10 micrograms (mcg)/hour (hr) and titrated upward to a maximum of 40 mcg/hr.[158] One study suggested efficacy for two-thirds of elderly OA patients (whose pain responds to opioids) at a seven-day low-dose buprenorphine patch at 5-20 mcg/hr when surgery was not possible and when NSAIDs were not recommended. Focus on and management of side effects is necessary.[159]

Buprenorphine has several properties that make it a potentially desirable as an analgesic. It is a synthetic opioid analgesic with partial mu opioid agonist and kappa opioid antagonist properties.[157] It has high affinity to the opiate receptor and a long duration of action (24-72 hr). Buprenorphine is a partial agonist agent and as such may be associated with less euphoria and easier withdrawal. Buprenorphine should not be added to patients that are on a full mu agonist as it will precipitate withdrawal. In addition, caution should be exercised when adding full mu agonists to patients on buprenorphine as the efficacy and side effect profiles may vary.

Pregnancy and liver disease require consideration of monotherapy (buprenorphine without naloxone). Other considerations for buprenorphine may be found in the VA/DoD SUD CPG.[11] Consideration should be given to specialty consultation when patients on buprenorphine have acute or post-operative pain conditions. Practitioners who prescribe SL buprenorphine or SL buprenorphine/naloxone for pain are not required to have an X Drug Enforcement Administration (DEA) number. However, practitioners do not need an X DEA license to prescribe buprenorphine patches labeled for pain. When buprenorphine is used for pain, higher doses should be used with caution in opioid-naïve patients. Split dosing is often preferred as the duration of pain relief may be 8-12 hr. All safety measures discussed in this guideline apply to buprenorphine products. For additional information, see Table 4 and Table 5 below.

Buprenorphine for Opioid Use Disorder

Patients on LOT may meet DSM-5 criteria for OUD. In addition, patients on LOT may have undiagnosed OUD that may manifest at the time of taper. The lifetime prevalence of any prescription OUD in patients on LOT may be as high as 41.3%.[160] In these cases, abrupt changes or discontinuation of the prescription opioid may result in increased risk of adverse events. Provision of SL buprenorphine may assist the provider and patient in meeting therapeutic goals for both pain and management of OUD. Specialty consultation is suggested in cases where pain and OUD are being treated concurrently. Further research is needed for managing patients with OUD and pain. There is substantial evidence for improved outcomes with MAT, which includes frequent drug use monitoring and counseling/psychotherapy at initiation of treatment in addition to medication (see Recommendation 17). Use of buprenorphine products for OUD is detailed in the VA/DoD SUD CPG.[11] Under the Drug Addiction Treatment Act of 2000 (DATA 2000), in order to prescribe buprenorphine for OUD, physicians must qualify for a physician waiver, which includes completing eight hours of required training and an application to SAMHSA.[161] Waivered physicians are provided with an X DEA number and there are limits regarding the number of patients that one provider can treat with buprenorphine for OUD.

[11] See the VA/DoD Clinical Practice Guideline for the Management of Substance Use Disorders. Available at: http://www.healthquality.va.gov/guidelines/mh/sud/index.asp

Table 4. Buprenorphine Formulations [162]

Route	Dosage Form	Strengths	Brand Name	Use
Topical	Transdermal System	5 mcg/hr 7.5 mcg/hr 10 mcg/hr 15 mcg/hr 20 mcg/hr	Butrans®	Management of pain severe enough to require around-the-clock, long-term, opioid treatment and for which alternative treatment options are inadequate
Buccal	Film	75 mcg 150 mcg 300 mcg 450 mcg 600 mcg 750 mcg 900 mcg	Belbuca®	Management of pain severe enough to require around-the-clock, long-term, opioid treatment and for which alternative treatment options are inadequate
Parenteral	Injection	0.3 mg/mL	Buprenex®	Management of moderate-to-severe pain
Sublingual	Tablets	2 mg 8 mg	Subutex®	Treatment of opioid dependence

Abbreviations: hr: hour(s); mcg: microgram(s); mg: milligram(s); mL: milliliter(s)

Table 5. Buprenorphine/Naloxone Formulations [162]

Route	Dosage Form	Strengths (listed as buprenorphine/naloxone)	Brand Name	Use
Buccal	Film	2.1 mg/0.3 mg 4.2 mg/0.7 mg 6.3 mg/1.0 mg	Bunavail®	Treatment of opioid dependence
Sublingual	Film	2 mg/0.5 mg 4 mg/1 mg 8 mg/2 mg 12 mg/3 mg	Suboxone®	Treatment of opioid dependence
Sublingual	Tablets	2 mg/0.5 mg 8 mg/2 mg	generic	Treatment of opioid dependence
Sublingual	Tablets	1.4 mg/0.36 mg 2.9 mg/0.71 mg 5.7 mg/1.4 mg 8.6 mg/2.1 mg 11.4 mg/2.9 mg	Zubsolv®	Treatment of opioid dependence

Abbreviations: hr: hour(s); mg: milligram(s)

Methadone

There is insufficient evidence to recommend methadone over other opioids for the treatment of chronic pain.[163] The only study included in the evidence review was limited to patients with cancer pain and suggested greater adverse effects with methadone than with other opioids.[166] An epidemiologic study suggests that the use of methadone contributes disproportionately to opioid overdose deaths relative to the frequency with which methadone has been prescribed.[164]

An analysis of opioid prescriptions by VA from 2010 to 2012 concluded that the prescribing of any long-acting/ER opioid medication, including methadone, was predictive of overdose or serious opioid-induced respiratory depression.[165] Studies comparing treatment of pain with methadone to treatment with other opioids describe inconsistent results and indicate that the risks associated with use of methadone vary greatly with treatment settings and management, monitoring, and risk mitigation strategies. A retrospective study of Tennessee Medicaid records (for years 1997 to 2007), documented an increased risk for overdose for non-institutionalized patients with non-cancer pain receiving methadone, including at low dosages.[166] A retrospective cohort study among Oregon Medicaid recipients (for years 2000 to 2004) found no statistically significant differences between methadone and long-acting morphine in risk for death. However, for the subgroup of patients with non-cancer pain, methadone was associated with greater risk of overdose symptoms, but not mortality or hospitalization.[167] A retrospective observational study of a large cohort drawn from VA healthcare databases (for years 2000 to 2007) documents that propensity-adjusted mortality was lower for methadone than for morphine. The study found no evidence of excess all-cause mortality among VA patients who received methadone compared with those who received long-acting morphine.[168]

Yet the unique pharmacologic properties of methadone make it particularly risky to prescribe. Methadone carries a risk of cardiac arrhythmia, and risk assessment for QT prolongation and electrocardiographic monitoring is essential. Methadone has a variable half-life with peak respiratory depressant effect occurring later and lasting longer than peak analgesic effect. Dose escalation to improve pain relief may lead to unintentional intoxication and corresponding respiratory depression or arrest.[166] Additionally, the metabolism of methadone varies by dose and individual, making dosing unpredictable. Plus, there are medications that interact with methadone and should not be prescribed concurrently (see Table D-2).

Only clinicians who are experienced with methadone and who are prepared to implement appropriate precautions, risk mitigation strategies, and patient/caregiver education should initiate, titrate, or taper methadone for chronic pain. Prescribers and patients should be familiar with these unique characteristics and institute appropriate safety precautions.

Specific guidance for clinicians about the risks of methadone is summarized below and detailed in Appendix D:

- Monitoring for cardiotoxicity [169]
  - Inform patients of the arrhythmia risk
  - Ask patients about heart disease, arrhythmia, and syncope
  - Obtain baseline ECG and regularly thereafter in intervals appropriate to risk/dosage
  - If the QTc interval is greater than 450 ms, but less than 500 ms, reevaluate and discuss with the patient the potential risks and benefits of therapy and the need for monitoring the QTc more frequently
  - If the QTc interval exceeds 500 ms, discontinue or taper the methadone dose and consider using an alternative therapy; other contributing factors, such as drugs that cause hypokalemia or QT prolongation, should be eliminated whenever possible

  - Be aware of interactions between methadone and other drugs that may prolong QTc interval or slow the elimination of methadone, and educate patients about potential drug interactions
- Conservative dosing
  - Methadone should not be initiated in opioid-naïve patients in the outpatient setting
  - Primary care clinicians should never rotate from another opioid to methadone without guidance from an experienced clinician regarding the starting dose of methadone
  - When initiating or increasing dosage, close follow-up is recommended (e.g., within five to seven days) to assess signs of methadone toxicity, such as excess sedation or delirium
  - Wait at least one week on a particular dose of methadone before increasing dosage of methadone to make sure that the full effects of the previous dosage are evident

Recommendations

14. We recommend tapering to reduced dose or to discontinuation of long-term opioid therapy when risks of long-term opioid therapy outweigh benefits.
    (Strong for | Reviewed, New-added)

    Note: Abrupt discontinuation should be avoided unless required for immediate safety concerns.

15. We recommend individualizing opioid tapering based on risk assessment and patient needs and characteristics.
    (Strong for | Reviewed, New-added)

    Note: There is insufficient evidence to recommend for or against specific tapering strategies and schedules.

Discussion

Clinicians should reassess the use of LOT in all patients currently receiving the therapy and consider tapering or discontinuing opioids in all patients on LOT when the risks exceed the benefits of therapy. Treatment of chronic pain with LOT in general is associated with considerable risk and must be justified by attainment of benefit that outweighs those risks in any individual patient. Non-pharmacologic therapies and non-opioid pharmacologic therapies are preferred and should be optimized. See Recommendation 1 for additional information on recommended treatments for chronic pain.

Observational studies (not included in the evidence review) suggest that when opioids are tapered or discontinued within the context of a multi-modal pain rehabilitation care plan, patients can experience an improvement in their pain, function, and mood.[170,171] Although the confidence in the quality of the evidence was low, the Work Group's determination that the benefits of individualized tapering of OT (when risks of LOT outweigh benefits) greatly outweigh the harms of tapering, as well as their consideration of individual patients' values and preferences, supported strong recommendations.

Indications for Tapering

If risks of OT outweigh benefits, OT should be tapered to a reduced dose or tapered to discontinuation. In the context of shared decision making, patient-specific goals, values, and preferences, the following should

be taken into consideration when determining the balance of risks and benefits of OT, recognizing that multiple risk factors increase cumulative risk:[172,173]

- Concomitant use of medications that increase risk of overdose
- Co-occurring medical or mental health conditions that increase risk
- Concerns about OUD or other SUD
- Patient adherence with opioid safety measures and opioid risk mitigation strategies
- Patient non-participation in a comprehensive pain care plan
- Prescribed dose higher than the maximal recommended dose (which increases risk of adverse events) (see Recommendations 10-12)
- Pain condition not effectively treated with opioids (e.g., back pain with normal magnetic resonance imaging [MRI]; fibromyalgia)
- Improvement in the underlying pain condition being treated
- Lack of clinically meaningful improvement in function
- Unmanageable side effects

When there is strong concern for diversion, opioids should be discontinued. For all patients, the prescribing clinician should regularly inquire about the patient's preference to taper OT to a reduced dose or discontinuation and explore ambivalence. OT should be tapered when patients voice their preference to reduce dosage and/or discontinue LOT.

There is large variation in patient preferences regarding continuing versus tapering OT and regarding the various processes that can be used when tapering opioids. Participants in the patient focus group expressed concern that when patients are receiving LOT, they may experience impaired judgement regarding decisions about opioid discontinuation due to the reinforcing nature of OT. Patients, therefore, may benefit from the outside perspective of their family members and healthcare providers. Such involvement should occur in accord with patient's preferences and within applicable privacy requirements (see Patient Focus Group Methods and Findings).

Low frequency of follow-up in primary care and limited access to comprehensive interdisciplinary specialty pain, rehabilitation, mental health, and addiction services may be barriers to tapering LOT that may need to be addressed.

Assessment/Follow-up

A biopsychosocial assessment including evaluation of medical, psychiatric, and co-occurring substance use conditions, as well as the patient's social support system, should be completed prior to the initiation of an opioid taper. The risks and benefits of the current opioid regimen should be weighed with the risks and benefits associated with a reduction in opioid dose. Periodic re-evaluation of risks and benefits coupled with a biopsychosocial assessment should occur when implementing an opioid taper and on follow-up. The frequency and type of follow-up is determined by risk assessment performed by the healthcare team. Follow-up should occur within a range of one week to one month after any opioid dosage change. Each follow-up interaction with the patient is an opportunity to provide education about self-management

strategies and the risks associated with OT while optimizing whole person approaches to pain care and treatment of co-occurring medical and mental health conditions. Following discontinuation of opioids, consider continuing risk mitigation strategies. Tapering may unmask underlying OUD. Therefore, frequent assessment for OUD is recommended (for more information on diagnosis and treatment of OUD see the VA/DoD SUD CPG).[12]

Referral

Clinicians should consider using an interdisciplinary, team-based approach that may include primary care, mental health, pain specialty/rehabilitation, pharmacy, physical therapy, and/or SUD services during the opioid tapering process. The treatment setting should be selected based on safety and the availability of services while also incorporating patient preferences.

It is important to recognize that some patients who are undergoing an opioid taper may experience symptoms of OUD that were not present or had not been previously identified prior to the taper. Opioid prescribers and the treatment team should remain vigilant for signs and symptoms of OUD for patients receiving LOT; particular attention is warranted during the tapering process. When there is concern for OUD or other SUD in a patient undergoing opioid tapering, clinicians should recommend SUD assessment and treatment to the patient in a setting that corresponds to the patient's level of risk and availability of services, while considering patient preferences (see the VA/DoD SUD CPG).[12] The possibility exists that some patients may be able to be seen in the primary care setting while others may be more appropriate for specialty care.

Patients on LOT with OUD are at increased risk of overdose when opioids are either continued or discontinued without appropriate treatment for OUD. We recommend MAT for OUD (e.g., MAT using methadone, buprenorphine/naloxone, or ER injectable naltrexone) (see the VA/DoD SUD CPG[12] and Recommendation 17). Treatment of OUD with MAT can occur in SUD programs as well as in primary care, specialty pain care, and mental health settings when the necessary resources are available. In patients with OUD, the opioid prescriber should ensure that OEND has been offered. The opioid prescriber may consider slowing the taper until a smooth hand-off to OUD treatment can be accomplished; however, close monitoring must occur for all patients during this transition process. Expediting the taper process and continuing to offer OUD treatment may be appropriate in some situations (e.g., if patient is not adherent to opioid taper and declines OUD treatment).

Additionally, underlying mental health disorders may be exacerbated by opioid use and/or opioid tapering and may require ongoing interdisciplinary care that includes mental health services.

The care team should take great efforts to ensure that the patient does not feel abandoned during the opioid tapering process. This includes clear communication with the patient that the care team will

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[12] See the VA/DoD Clinical Practice Guideline for the Management of Substance Use Disorders. Available at: http://www.healthquality.va.gov/guidelines/mh/sud/index.asp

maintain frequent contact with the patient during the opioid taper and emphasizing that the care team will continue to pursue non-opioid pain care options during and after opioid tapering.

Clinicians should also educate the patient/family about acute and protracted opioid withdrawal symptoms and provide treatment strategies to mitigate these symptoms as appropriate.[174] To foster patient engagement with the taper plan, clear written and verbal instructions should be given to the patient/family regarding the tapering protocol, strategies to mitigate withdrawal symptoms, and additional non-opioid treatments for the patient's pain condition.

> Strongly caution patients that it takes as little as a week to lose tolerance to their prior opioid dose and that they are at risk of an overdose if they resume their prior dose.

Regardless of the initial speed of taper, the rate of taper may need to be adjusted during the course of lowering the opioid dose. The pace of taper should be reevaluated after each dose change.

If patients are receiving both long-acting and short-acting opioids, the decision regarding which formulation to be tapered first needs to be individualized based on safety, medical history, mental health diagnoses, and patient preference. However, it should be kept in mind when making this decision that long-acting opioids may be associated with higher overdose, overdose death, and all-cause mortality rates when compared to short-acting opioids, which may suggest tapering long-acting opioids first.[10,137] There may also be times when tapering both formulations simultaneously is appropriate.

If an opioid dose reduction is the initial treatment goal, ongoing assessment of the balance of risks and clinically meaningful benefits should be performed once the original treatment goal is achieved. If this assessment determines that the benefits of continuing OT do not outweigh risks, additional dose reduction and/or tapering to discontinuation should be pursued.

Tapering Process

The goal of opioid tapering is to improve the balance of risks and clinically meaningful benefits for patients on LOT. The risks and benefits of the current opioid regimen should be weighed with the risks and benefits associated with a reduction in opioid dose. If the provider determines a patient to be at significant risk of adverse outcomes due to the use of LOT, and if either the patient or the clinician is concerned about potential destabilizing effects of opioid tapering, referral to, or consultation with, specialty services including mental health, SUD, pain medicine, and rehabilitation should be strongly considered.

Abrupt discontinuation of opioids may be justified in certain high-risk circumstances. When there is evidence for diversion, the clinician may need to discontinue OT, frequently assess for withdrawal symptoms, and offer necessary support for withdrawal symptoms and treatment of SUD, if present. When a patient exhibits dangerous behaviors (e.g., threatening behaviors, persistent and serious disruptive behavior, suicidal ideation or behaviors), the clinician may consider abruptly discontinuing OT while providing urgent or emergent psychiatric referral and medical care for the management of opioid withdrawal. When relevant, dangerous or illegal behavior should be documented accurately and completely in the EMR to guide future care. When ongoing pain is suspected, non-opioid treatment for pain should be implemented.[175]

The characteristics that will determine the speed of tapering include opioid dose, duration of therapy, type of opioid formulation, and co-occurring psychiatric, medical, and substance use conditions. The tapering treatment plan should be individualized and should address the pace of tapering, setting of care, and frequency of follow-up. When determining the pace of opioid tapering, factors that would suggest a more gradual taper include higher opioid dose and longer duration of OT; factors that would suggest a more rapid taper include non-adherence to the treatment plan and escalating high-risk medication-related behaviors. When safety permits, gradual tapers are often better tolerated. In addition, for some patients, pauses in the taper for weeks or months may allow the patient time to acquire new skills for management of pain and emotional distress while also allowing time for neurobiological equilibration.

The rate of taper takes into account many factors that include initial dose, formulations available, and risk factors that increase harm. A gradual taper over months or even years for patients starting on very high opioid doses involves reducing by 5-20% every four weeks. In some patients, a faster taper may be needed when risks are too high to consider a gradual taper; consider tapering the dose by 5-20% per week in this patient population.

When it is determined that patient risks are significantly high to warrant a rapid taper over a period of days or weeks, then specialty consultation should be obtained to determine the rate of taper and resources needed. These patients will need frequent follow-up and reevaluation of SUD, mental health, and/or co-occurring medical conditions with every dose change.

Patients Receiving Very High Dose Opioid Therapy

For patients currently prescribed ≥90 mg MEDD, a comprehensive assessment that recognizes the increased risk of high dose OT should be performed. Tapering to a reduced dose or tapering to discontinuation should be pursued when clinically meaningful functional benefit is not demonstrated or when significant risk factors in addition to the prescribed opioid dose are present. It should be recognized that elevated dose alone poses increased risk of overdose, overdose death, adverse effects, and the development of OUD. Assessing clinically meaningful functional benefit should be individualized and incorporate the use of SMART goals and considered in the context of patient-specific goals, values, and preferences (see table Guide in Setting SMART Goals).

Mental health and SUD comorbidities that were previously unrecognized or that may worsen should be assessed and addressed with an interdisciplinary approach. Interdisciplinary care including mental health, rehabilitation, and SUD treatment services may be necessary to support the tapering process. Use of MAT, which includes behavioral approaches, should be offered for patients in whom a diagnosis of OUD is made (see the VA/DoD SUD CPG).[13]

[13] See the VA/DoD Clinical Practice Guideline for the Management of Substance Use Disorders. Available at: http://www.healthquality.va.gov/guidelines/mh/sud/index.asp

Naloxone

Overdose education should be provided and naloxone should be offered as an antidote to all patients at risk for an opioid overdose including those who are in the process of tapering. During and following an opioid taper, patients may still be using opioids from other sources such as saved opioids, other prescribers, friends and family, as well as illicit sources. Continued surveillance for OUD and assessment for naloxone is suggested in patients who are no longer on opioids but who remain at risk for opioid use from unknown sources. For more information, see Recommendations 7-9.

Future Research

Additional research is needed to identify the opioid tapering processes that are associated with the best patient outcomes among a broad range of domains including general functioning, psychosocial functioning, mood, pain related disability, and adverse outcomes assessed in the short, medium, and long-term.

Recommendation

16. We recommend interdisciplinary care that addresses pain, substance use disorders, and/or mental health problems for patients presenting with high risk and/or aberrant behavior. **(Strong for| Reviewed, New-replaced)**

Discussion

A variety of high-risk medication-related behaviors (e.g., early refills, lost or stolen medications, problematic findings on urine tests) may suggest the presence of SUD (also known as opioid addiction, abuse, or dependence). Non-adherence to treatment plans or repeated failure to show for clinic appointments can add to the challenge of safely providing LOT in the primary care setting. The presence of co-occurring SUD or psychiatric conditions in some patients can make prescribing LOT an overwhelming problem for primary care providers. Chronic pain is a complex human experience influenced by physical, psychological, and social factors. Multidisciplinary care that addresses these influences is helpful for all patients, but is absolutely essential when pain is accompanied by co-occurring conditions, impaired function, or psychological problems.

Low quality evidence supports the benefits of providing brief behavioral interventions and close monitoring to patients at high risk for prescription opioid misuse.[114] Some evidence suggests that patients referred to highly structured opioid-renewal programs that provide patients with frequent UDT monitoring, frequent clinic visits, smaller quantities of medications, and ongoing counseling/education is helpful for patients and primary care providers. Meghani et al. (2009) found that high-risk medication-related behaviors resolved in 45.6% of patients managed in a pharmacist-run opioid renewal clinic.[176] Although the confidence in the quality of the evidence was low, the Work Group's determination that the benefits of interdisciplinary care for patients with pain and other comorbidities (e.g., SUD, mental health problems) contributed to a strong recommendation.

Consider referring patients with co-occurring substance use or psychiatric conditions to addiction medicine/psychiatry or other behavioral health specialists. Coordination of care between pain care and other specialty care, including SUD clinicians, is advised. If structured comprehensive programs are not available, coordination among individual healthcare providers is essential to address the full range of high-

risk behaviors. Chronic pain in general, and LOT in particular, requires consideration of all of the patient's life problems. If resources do not exist to address co-occurring SUD and psychiatric conditions or if the patient declines to participate, treatment with LOT should be reconsidered.

Research is needed to identify the efficacy and feasibility of providing multidisciplinary care to patients demonstrating significant high-risk medication-related behaviors when prescribed LOT in primary care settings.

Recommendation

17. We recommend offering medication assisted treatment for opioid use disorder to patients with chronic pain and opioid use disorder.
    (Strong for | Reviewed, New-replaced)

    Note: See the VA/DoD Clinical Practice Guideline for the Management of Substance Use Disorders.

Discussion

OUD (also known as opioid addiction, abuse, or dependence) is a chronic brain disease that impairs one's ability to control opioid use. Opioids disrupt the functioning of brain circuits that mediate a complex array of functions involved in obtaining natural rewards such as food and water that are essential for survival. Because opioids activate these circuits more powerfully than natural rewards, the primitive brain learns to prioritize attention to and motivation for opioids over other natural rewards.[177] Repeated opioid use over time can lead to OUD. While there are some risk factors such as other substance use or co-occurring mental illness that can increase the risk of developing an OUD among those taking opioid analgesics, by far the most powerful risk factor for developing OUD is long-term opioid analgesics use. All persons using opioid analgesics are at-risk for developing an OUD. Persons who become addicted to opioids gradually become more and more preoccupied with opioid use and spend more of their time seeking the drug, using it, or recovering from its effects. They may continue to use opioids even though they:

- Know that opioid use is harmful
- Often use more than they intended
- Engage in risky behaviors such as driving while intoxicated or combining opioids with alcohol or other sedatives
- Have multiple unsuccessful attempts to cut down or control opioid use
- Report strong craving or urges to use opioids in response to withdrawal symptoms, stress, negative emotions, or simply cues that the drug is available

OUD is associated with premature death from opioid overdose and other medical complications such as acquired immunodeficiency syndrome (AIDS), hepatitis C, and sepsis. On average, OUD carries a 40-60% 20-year mortality rate.[178] Persons with OUD are at high-risk for premature death, not only from opioid

overdose, but from other consequences. Thus, providing first-line treatment is important to save lives as well as to improve the quality of life of patients.

Strong evidence supports the use of opioid agonist therapy (e.g., methadone, buprenorphine/naloxone) as first-line treatment for moderate-to-severe OUD (see VA/DoD SUD CPG).[14] However, because this research has been conducted primarily on persons addicted to heroin, the populations studied have had a higher prevalence of co-occurring SUD and lower prevalence of chronic pain. Patients and their treating clinicians may be concerned that treatments proven effective in different OUD populations may not be effective for patients with chronic pain, or may not be necessary for patients who have become addicted to prescription opioid analgesics. This concern has been unfounded and was addressed by Weiss and colleagues in the Prescription Opioid Abuse Treatment Study (POATS).[179]

Early research suggested that patients with prescription OUD may have a better prognosis than those who are primarily addicted to heroin, implying that those with prescription OUD may not need MAT.[180,181] However, in studies with patients with DSM-IV opioid dependence (which were conducted prior to use of DSM-5), buprenorphine maintenance therapy is more effective than a four-week taper. One multicenter RCT tested the hypothesis that patients with prescription OUD would respond well to a four-week tapering of buprenorphine/naloxone to discontinuation plus two regimens of outpatient counseling.[179] Those who did not achieve successful outcomes after buprenorphine taper in phase one were invited to participate in phase two consisting of 12-weeks treatment using buprenorphine/naloxone followed by taper to discontinuation. During both phases, patients were randomized to receive a manualized, physician-delivered psychosocial intervention known as Standard Medical Management or Standard Medical Management plus manually-driven opioid drug counseling delivered by a trained therapist. Only 6.6% of these patients achieved a successful outcome after tapering in phase one with no difference between the groups. In phase two, while taking buprenorphine/naloxone, 49% of patients achieved a successful outcome again with no difference between the counseling groups. Eight weeks after tapering again, only 8.6% of patients achieved a successful outcome. This suggests that MAT with moderate dose buprenorphine/naloxone and brief, structured counseling by the prescribing physician can be successful for about half of selected patients with prescription OUD, whereas withdrawal management alone, even with close weekly follow-up and counseling is successful for less than 10% of patients.

Furthermore, the presence of chronic pain does not seem to interfere with the success of MAT. The RCT by Weiss et al. (2011) and a meta-analysis by Dennis et al. (2015) reached the same conclusion that the presence of chronic pain did not influence response to opioid agonist therapy.[179,182] Given the high mortality associated with OUD and the safety and efficacy of MAT for OUD in multiple clinical trials and meta-analyses, we recommend MAT for those chronic pain patients who meet DSM-5 criteria for OUD. Those who do not respond to minimal counseling may benefit from a comprehensive assessment and more intensive treatment of OUD and any co-occurring conditions in SUD specialty care settings.

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[14] See the VA/DoD Clinical Practice Guideline for the Management of Substance Use Disorders. Available at: http://www.healthquality.va.gov/guidelines/mh/sud/index.asp

D. Opioid Therapy for Acute Pain

Recommendation

18. a) We recommend alternatives to opioids for mild-to-moderate acute pain. **(Strong for)**
    b) We suggest use of multimodal pain care including non-opioid medications as indicated when opioids are used for acute pain. **(Weak for)**
    c) If take-home opioids are prescribed, we recommend that immediate-release opioids are used at the lowest effective dose with opioid therapy reassessment no later than 3-5 days to determine if adjustments or continuing opioid therapy is indicated. **(Strong for)**
    (Reviewed, New-added)

    Note: Patient education about opioid risks and alternatives to opioid therapy should be offered.

Discussion

As this guideline is related to LOT, the use of opioids for acute pain is not reviewed in detail. However, because acute OT can be a gateway to LOT, it is part of this CPG. A review of the literature indicates that LOT can result from acute opioid use initially intended for short-term therapy. Further, there is a risk of opioid-related overdose even during acute OT. While it is understood that acute OT for severe pain due to injuries or surgery is the most effective option for many patients, the risks associated with acute therapy must be addressed when opioids are prescribed or considered.

The risks of acute OT extending into LOT are increased in patients with mood disorders, those who refill the initial prescription, higher prescribed dose (greater than 120 mg MEDD), and initiation using long-acting opioids.[183-185] The risk of acute post-operative OT progressing into LOT is increased with a history of depression, SUD, catastrophizing, higher preoperative total body pain, history of back pain, and preoperative use of sedative-hypnotics or antidepressants.[186,187]

In addition, the risk of overdose includes the use of opioids for acute pain. Factors that increase overdose risk when opioids are used for acute pain include high prescribed dose, history of SUD, and history of mental health concerns. While the risk of overdose increases at doses above 20 mg MEDD or greater, this risk increases even further as doses increase to over 50 or 100 mg MEDD.[58,59,188]

There are situations in which opioids may be necessary therapy for acute pain, even when substantial risk factors exist. It is important to incorporate opioid risk mitigation strategies into opioid prescribing for acute pain. These strategies should include patient education, use of non-opioid adjunctive therapy, and structured reassessment of opioid risks and benefits for all on acute OT. Also, consider checking the PDMP and performing a UDT.

For those at higher risk of adverse events related to opioid therapy, the following strategies may help to decrease opioid-related overdose events and unintended long-term use: checking the PDMP, performing a UDT, placement in an inpatient setting or monitored environment, and/or providing OEND.

Monitoring standards with administration of OT for acute pain vary depending on a number of factors including the setting, specifics of the painful insult, patient medical factors, and selected medication potency/dose/route of administration/adjunct selection.

Appendix A: VA Signature Informed Consent

For the most current information on informed consent, see the VA National Center for Ethics in Health Care website (http://www.ethics.va.gov/).

Department of Veterans Affairs	Consent for Long-Term Opioid Therapy for Pain	
A. IDENTIFICATION		
1. Patient Name, Social Security Number, and Date of Birth:		
Name: Last, First, Middle	Social Security Number	Date of Birth
2. Decision-making capacity:		
☐ The patient HAS decision-making capacity (skip to item 3).		
☐ The patient DOES NOT HAVE decision-making capacity. Enter surrogate name and relationship to the patient. (If the patient's surrogate is not established or available, refer to Handbook 1004.01 for guidance).		
Name: Last, First, Middle	Relationship	
3. Name of the treatment: Long-Term Opioid Therapy for Pain		
4. Practitioner obtaining consent:		
Name: Last, First, Middle		
5. Supervising practitioner: (if applicable)		
Name: Last, First, Middle		
6. Additional practitioner(s) performing or supervising the treatment: (if not listed above)		
B. INFORMATION ABOUT THE TREATMENT		
7. Reason for long-term opioid therapy (diagnosis, condition, or indication):		
8. Location of pain:		
9. Goal(s) of long-term opioid therapy (e.g., pain score, functional abilities such as go back to work, climb stairs, walk short distances, sleep through the night, do daily household chores, start a light exercise program):		
10. Name of current or initial opioid medication(s):		

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11. Brief description of the treatment:

Opioids are very strong medicines that may be used to treat pain. You may already be taking opioids. Or your provider may try to give you opioids to find out if they will help you. They may try them for a short time or continue them for the rest of your life. Your provider will learn more about your risks and side effects when you are trying the opioids. If the risks and side effects outweigh the benefits, your provider will stop the prescription.

If your provider continues your opioid prescription, the goals of your treatment may change over time. The names and doses of your opioids may also change. You will not need to sign another consent form for these changes. You may be asked to sign another consent form if you seek opioid pain care from another VA provider.

Your provider will monitor your prescription. This may include checking how often you refill and renew your prescription, counting pills, asking you about your symptoms, and testing your urine, saliva, and blood. If you do not take opioids responsibly, your provider may stop your prescription. For example, if you do not let your provider monitor how you are responding to the opioids or tell them if you are taking other drugs that may affect the safety or effectiveness of your opioid treatment, your provider may stop the prescription.

For your safety, your provider and pharmacist will monitor when you renew and refill your opioids within VA. Consistent with state law, they will also monitor this outside of VA. Most states have monitoring programs that track unsafe patterns of prescription drug use. VA and these programs may obtain and share information about you without your specific consent.

Your provider will review with you a Patient Information Guide called "Taking Opioids Responsibly" to make sure that you know how to take your medication safely. You will be given a copy of the guide so that you can use it as a reference

12. Potential benefits of the treatment:

Opioids -- when added to other treatments as part of your pain care plan -- may reduce your pain enough for you to feel better and do more. It is unlikely that opioids will eliminate your pain completely. It is possible that you may not receive any benefits from opioid therapy.

13. Known risks and side effects of the treatment:

Possible opioid side effects include:

- Sleepiness or "slow thinking"
- Mental confusion, bad dreams, or hallucinations
- Constipation
- Intestinal blockage
- Itching
- Sweating
- Nausea or vomiting
- Decreased sex hormones
- Irregular or no menstrual periods
- Depression
- Dry mouth that causes tooth decay
- Allergies

Other risks of opioid therapy:

- Withdrawal symptoms if you suddenly stop taking opioids, lower the dose of your opioids too quickly, or take a drug that reverses the effects of your opioids. Withdrawal symptoms are caused by physical dependence that is a normal result of long-term opioid therapy. Some common withdrawal symptoms are runny nose, chills, body aches, diarrhea, sweating, nervousness, nausea, vomiting, mental distress, and trouble sleeping.
- Sleep apnea (abnormal breathing pauses during sleep)
- Worsening of pain
- Impaired driving or impaired ability to safely operate machinery
- Tolerance, which means that you may need a higher dose of opioid to get the same pain relief, resulting in an increase in the likelihood of the other side effects and risks
- Addiction (craving for a substance that gets out of control). Some patients become addicted to opioids even when they take opioids as prescribed.
- Drug interactions (problems when drugs are taken together). Taking small amounts of alcohol, some over-the counter medications, some herbal remedies, and other prescription medications can increase the chance of opioid side effects.
- Risks in pregnancy:
  - ***Continued use of opioids during pregnancy can cause your baby to have withdrawal symptoms after birth and require your baby to stay in the hospital longer after birth.**
  - ***Stopping opioids <u>suddenly</u> if you are pregnant and physically dependent on opioids can lead to complications during pregnancy.**
  - ***Studies have not shown a clear risk for birth defects with opioid use in pregnancy. If there is an increased risk for birth defects in pregnancy with opioid use, it is likely small.**
- Death

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14. Alternatives to the treatment:

You have the option not to take opioids. Other treatments can be used as part of your pain care plan. Alternatives include:

- Heat and cold therapy (heating pads, ice packs)
- Stretching
- Exercise
- Weight loss
- Massage
- Acupuncture
- Chiropractic
- Nerve Stimulation
- Relaxation or stress reduction training
- Physical therapy
- Occupational therapy
- Mental health treatment
- Self-care techniques
- Counseling and coaching
- Meditation
- Rehabilitation
- Non-opioid pain medicines (Non-steroidal anti-inflammatory drugs, antidepressants, anticonvulsants)
- Injections
- Specialist pain care
- Surgery
- Pain classes
- Support groups
- Attention to proper sleep

15. Additional Information:

16. Comments:

C. SIGNATURES

Practitioner obtaining consent:

- All relevant aspects of the treatment and its alternatives (including no treatment) have been discussed with the patient **(or surrogate) in language that s/he could understand. This discussion included the nature, indications, benefits, risks, side effects, monitoring, and likelihood of success of each alternative that was considered.**
- I have discussed all of the information contained in the education document "Taking Opioids Responsibly" with the patient (or surrogate).
- The patient (or surrogate) demonstrated comprehension of the discussion.
- I have given the patient (or surrogate) an opportunity to ask questions.
- I did not use threats, inducements, misleading information, or make any attempt to coerce the patient/surrogate to consent to this **treatment.**
- I have offered the patient (or surrogate) the opportunity to review and receive a printed copy of the consent form.
- If the patient is a woman of childbearing age (ages 15-50), I have discussed the patient's pregnancy status and pregnancy intentions.
  - **If the patient is not considering pregnancy, I have discussed (or referred the patient for) contraceptive counseling.**
  - **If the patient is considering pregnancy, I have discussed (or referred the patient for) preconception counseling.**

Signature _____ Date _____ Time _____

Patient or surrogate:

- I understand that to receive long-term opioids I must agree to my opioid treatment plan by signing this consent form.
- Someone has explained the treatment, what it is for, and how it could help me.
- Someone has explained things that could go wrong, including serious side effects and death, particularly if I do not take my medicine as prescribed.
- Someone has told me about other treatments that might be done instead, and what would happen if I have no treatment.
- I have discussed the information in the document "Taking Opioids Responsibly" with my provider.
- I understand the importance of:
  - **telling my provider about side effects.**
  - **telling my provider about changes in my pain and daily function.**
  - **getting my opioids from only my VA provider and no one else.**
  - **not giving away (or selling) my opioids to other people.**
  - **storing my opioids in a safe place away from children, family, friends, and pets.**
  - **safely getting rid of opioids I do not need.**
  - **not drinking alcohol or taking illegal street drugs when I am on opioids.**
  - **for women, telling my provider if I think I might be pregnant, know I am pregnant, or am planning to become pregnant.**

- I plan to use my medications responsibly, and take them as prescribed.
- I understand how to refill my opioid prescription or get a new prescription. I understand that my VA pharmacy may be closed on weekends, holidays, and after regular clinic hours. I understand that my provider might not give me early medication refills or replace doses that are lost or stolen.
- I understand that my provider may order urine or blood drug tests with my consent (separate from this consent). I understand that the results of these tests or my refusal to be tested may cause my provider to talk to me about changing my opioid treatment plan.
- I understand that I may have to stop opioids if my provider thinks that it is unsafe for me to continue.
- Someone has answered all my questions.
- Someone has given me information about how to contact the clinic, if there is a problem and who to call in an emergency.
- I know I may refuse or change my mind about having treatment. If I do refuse or change my mind, I will not lose my health care or any other VA benefits.
- I have been offered the opportunity to review and receive a copy of my consent form.
- I choose to have this treatment.

Signature _____ Date _____ Time _____

Witnesses: No witness is required if the patient or surrogate signs their name. Two witnesses are required only when the patient's signature is indicated with an "X" or some other identifying mark.

Witness Name (Please Print) _____

Witness Signature _____ Date _____ Time _____

Witness Name (Please Print) _____

Witness Signature _____ Date _____ Time _____

Appendix B: Urine Drug Testing

A. Benefits of Urine Drug Testing

Substance misuse in patients on LOT is more than 30% in some series.[107] The inaccuracies inherent to patient self-report coupled with the evident mortality and morbidity to the treated patients, their families, and others require additional methods to ascertain patient and public safety. UDT and confirmatory testing is an additional method of examining for patient substance misuse and adherence to the prescribed regimen as well as the development of trust within the provider-family-patient relationship. It is critical that the UDT and confirmatory testing be done in a timely, confidential, accurate, and easily available manner to assure the prescribers, patients, and public that safety, fairness, and trust are being addressed.

Within the VA, verbal informed consent is required prior to UDT. While a patient can decline to consent to UDT, a provider can factor that declination into their thinking about whether it is safe to continue with OT for that patient which is ultimately required if LOT is to be instituted/continued. For more information, see the VA National Center for Ethics in Health Care website (http://www.ethics.va.gov/).

B. Types of Urine Drug Testing

There are three main types of UDT currently being utilized in clinical settings: immunoassay, GCMS confirmatory testing, and liquid chromatography-mass spectrometry confirmatory testing. Immunoassay screening is inexpensive, fast and widely available. However, there are a number of drawbacks for using this test alone. There is a higher potential for false positives and negatives as well as lack of specificity of the actual opiate or benzodiazepine being tested. GCMS is highly sensitive and specific; however, it is expensive and time consuming. LCMS is less expensive than GCMS but more expensive than immunoassay. It can give a confirmation for a large number of medications, substances and drugs at one time and may be helpful in many patients at initiation of OT, periodically during OT, and following cessation of OT if SUD is a possibility. See Table B-1 through Table B-4 and Figure B-1 for more information.

Table B-1. Urine Toxicology Specimen Validity and Normal Characteristics of a Urine Sample [189-191]

Urine Toxicology Specimen Validity	Normal Characteristics of a Urine Sample
▪ Urine samples that are adulterated, substituted, or diluted may avoid detection of drug use ▪ Urine collected in the early morning is most concentrated and most reliable ▪ Excessive water intake and diuretic use can lead to diluted urine samples (creatinine<20 mg/dL) ▪ THC assays are sensitive to adulterants (e.g., eye drops)	Temperature within 4 minutes of voiding: 90-100°F
	pH: 4.5-8.0
	Creatinine: >20 mg/dL
	Specific gravity: >1.003
	Nitrates: <500 mcg/dL
	Volume: ≥30 mL

Abbreviations: °F: degrees Fahrenheit; dL: deciliter(s); mcg: microgram(s); mg: milligram(s); mL: milliliter(s); THC: tetrahydrocannabinol

Table B-2. Urine Toxicology Screening Federal Work Place Cut Off Values [189-195]

		Agent	Initial drug test level (immunoassay) (ng/mL)	Confirmatory drug test level (GCMS) (ng/mL)	Confirmatory test analyte	Detection Period after Last Dose (days)[1]
Extended UTS	Regular UTS	Marijuana metabolites	50	15	THCA	2-8 single use 20-30 chronic use[2]
		Cocaine metabolites	300	150	Benzyolyecgonine	1-3
		Opioid metabolites	2000[3]	2000[3]	Codeine Morphine 6-MAM	2-3 days opiates 3-5 minutes heroin 12-24 hr 6-MAM
		Oxycodone				2-4
		Amphetamines	1000	500	Amphetamine Methamphetamine MDMA, MDA, MDEA	1-3
		Methamphetamine	Incomplete data	500		3-4
		Benzodiazepines	300	200		3 short-acting 30 long-acting
		Barbiturates	300	200		1 short-acting 21 long-acting
		Methadone	300	200	EDDP	3-6
		Alcohol			EtG, EtS	12 hr

[1]Detection time for most drugs in urine is 1-3 days

[2]Long-term use of lipid-soluble drugs (THC, diazepam, ketamine) can be detected for a longer period of time

[3]Testing levels for opiates were raised from 300 ng/mL to 2000 ng/mL to reduce detection from foods containing poppy seeds

Abbreviations: 6-MAM: 6-monoacetylmorpine; EDDP: 2-ethylidene-1,5-dimethyl-3,3-diphenylpyrrolidine; EtG: ethyl glucuronide; EtS: ethyl sulfate; GCMS: gas chromatography-mass spectrometry; hr: hour(s); MDA: 3,4-methylenedioxy-amphetamine; MDEA: 3,4-methylenedioxy-N-ethyl-amphetamine; MDMA: 3,4-methylenedioxy-methamphetamine; mL: milliliter(s); ng: nanogram(s); THC: tetrahydrocannabinol; THCA: delta-9-tetrahydrocannabinol-9-carboxylic acid; UTS: urine toxicology screening

Table B-3. Summary of Agents Potentially Contributing to False Positives [189-194]

Agent	Summary of Agents Potentially Contributing to False Positives		
Marijuana metabolites	▪ dronabinol ▪ efavirenz	▪ NSAIDs[1] ▪ proton pump inhibitors	▪ hemp foods: tea, oil[2]
Cocaine metabolites	▪ coca leaf teas	▪ topical anesthetics containing cocaine	
Opioid metabolites	▪ dextromethorphan ▪ fluoroquinolones ▪ levofloxacin	▪ ofloxacin ▪ poppy seeds ▪ poppy oil	▪ rifampin ▪ quinine
Amphetamines/ Methamphetamine (high rate of false positives)	▪ amantadine ▪ benzphetamine ▪ brompheniramine ▪ bupropion ▪ chlorpromazine ▪ desipramine ▪ dextroamphetamine ▪ doxepin ▪ ephedrine ▪ fluoxetine	▪ isometheptene ▪ isoxsuprine ▪ labetalol ▪ l-methamphetamine (OTC nasal inhaler) ▪ methylphenidate ▪ MDMA ▪ phentermine ▪ phenylephrine	▪ propanolamine ▪ promethazine ▪ pseudoephedrine ▪ ranitidine ▪ selegiline ▪ thioridazine ▪ trazodone ▪ trimethobenzamide ▪ trimipramine
Benzodiazepines	▪ oxaprozin	▪ sertraline	
Barbiturates	▪ ibuprofen	▪ naproxen	
Methadone	▪ chlorpromazine ▪ clomipramine ▪ diphenhydramine	▪ doxylamine ▪ ibuprofen ▪ quetiapine	▪ thioridazine ▪ verapamil
Alcohol	▪ mouthwash	▪ short-chain alcohols	▪ OTC cough products (isopropyl alcohol)

[1]Detection time for most drugs in urine is 1-3 days

[2]Long-term use of lipid-soluble drugs (THC, diazepam, ketamine) can be detected for a longer period of time

Abbreviations: NSAIDs: non-steroidal anti-inflammatory drugs; MDMA: 3,4-methylenedioxy-methamphetamine; OTC: over the counter; THC: tetrahydrocannabinol

Table B-4. Interpreting Urine Toxicology Screening [189-191,196]

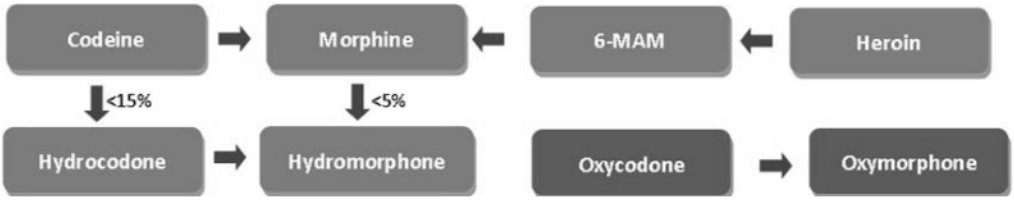
	Drug or Class	Expected Results	Considerations
Non-opioids	Alcohol	Alcohol	▪ Testing for ethanol metabolites, ethyl glucuronide or ethyl sulfate, can identify alcohol up to 80 hr after consumption
	Amphetamines	**Immunoassay** – Amphetamines, methamphetamines or MDMA **Confirmatory** – Amphetamines, methamphetamines or MDMA	▪ Immunoassay tests are highly cross-reactive; therefore confirmatory testing is required and can identify which amphetamine is present
	Benzodiazepines	**Immunoassay** – Unconjugated oxazepam or its metabolites **Confirmatory** – Alprazolam, diazepam, clonazepam, lorazepam, etc.	▪ Immunoassays for benzodiazepines have a 28% overall false negative rate ▪ Confirmatory testing is needed when use is expected or suspected (alprazolam, clonazepam and lorazepam often not detected by immunoassay)
	Barbiturates	**Immunoassay** – Barbiturates	▪ N/A
	Cocaine metabolites	**Immunoassay** – Cocaine or benzoylecgonine	▪ Cocaine's primary metabolite, benzoylecgonine, has low cross-reactivity with other substances and is highly predictive of cocaine use ▪ A positive result should be interpreted as recent exposure to cocaine
Opioids or "Opiates"-Natural (From Opium)	Codeine (Tylenol #2,3/4)	**Opiates Immunoassay** – Positive **Confirmatory** – Codeine, possibly morphine & hydrocodone	▪ Immunoassays for "opiates" are responsive to morphine and codeine but do not distinguish which ▪ Codeine is metabolized to morphine and small quantities of hydrocodone
	Morphine (Avinza, Embeda, MS Contin, Kadian)	**Opiates Immunoassay** – Positive **Confirmatory** – Morphine, possibly hydromorphone	▪ Immunoassays for "opiates" are responsive to morphine and codeine but do not distinguish which ▪ Morphine (<10%) may be metabolized to hydromorphone
	Heroin	**Opiates Immunoassay** – Positive **Confirmatory** – Heroin (6-MAM), morphine, possibly codeine	▪ 6-MAM is pathognomonic for heroin use, detection 12-24 hr ▪ Heroin is metabolized to morphine

	Drug or Class	Expected Results	Considerations
Opioids-Semisynthetic (Derived from Opium)	Hydrocodone (Lorcet, Lortab, Norco, Vicodin)	**Opiates Immunoassay** – Positive **Confirmatory** – Hydrocodone, possibly hydromorphone	▪ "Opiates" immunoassay may detect semisynthetic opioids ▪ hydrocodone >hydromorphone >oxycodone ▪ Negative result does not exclude use and confirmatory testing (GCMS) is required ▪ Hydrocodone is metabolized in small amounts to hydromorphone, both may be found in urine ▪ Oxycodone is metabolized to oxymorphone, both may be found in urine ▪ Hydromorphone and oxymorphone use does not result in positive screens for hydrocodone and oxycodone, respectively
	Hydromorphone (Dilaudid, Exalgo)	**Opiates Immunoassay** –May be positive **Confirmatory** – Hydromorphone	
	Oxycodone (Roxicet, OxyContin)	**Opiates Immunoassay** – May be positive **Oxycodone Immunoassay** – Positive **Confirmatory** – Oxycodone possibly oxymorphone	
	Oxymorphone (Opana)	**Oxycodone Immunoassay** – Positive **Confirmatory** – Oxymorphone	
Opioids – Synthetic (Man-made)	Buprenorphine	**Immunoassay** – Buprenorphine **LCMS, GCMS** – Buprenorphine, norbuprenorphine	▪ Current "opiates" immunoassays do not detect synthetic opioids ▪ Confirmatory testing (GCMS or LCMS) is needed
	Fentanyl	**GCMS** – Fentanyl, norfentanyl	
	Meperidine (Demerol)	**GCMS** – Normeperidine, possibly meperidine	
	Methadone (Methadose)	**Methadone Immunoassay** – Positive **GCMS** – Methadone, EDDP	

Note: Each facility may have its own order sets and lab policies and procedures. Contact your lab for additional details.

Abbreviations: 6-MAM: 6-monoacetylmorpine; EDDP: 2-ethylidene-1,5-dimethyl-3,3-diphenylpyrrolidine; GCMS: gas chromatography-mass spectrometry; LCMS: liquid chromatography-mass spectrometry; MDMA: 3,4-methylenedioxy-methamphetamine

Figure B-1. Opioid Metabolic Pathways [190-193]



Abbreviations: 6-MAM: 6-monoacetylmorpine

Appendix C: Diagnostic and Statistical Manual of Mental Disorders for Opioid Use Disorders

DSM-5 diagnostic criteria for OUD: A problematic pattern of opioid use leading to clinically significant impairment or distress, as manifested by at least two of the symptoms in Table C-1, occurring within a 12-month period.[197]

Table C-1: DSM-5 Diagnostic Criteria for OUD [197]

DSM-5 Diagnostic Criteria for OUD
1. Craving or strong desire or urge to use opioids
2. Recurrent use in situations that are physically hazardous
3. Tolerance
4. Withdrawal (or opioids are taken to relieve or avoid withdrawal)
5. Using larger amounts of opioids or over a longer period than initially intended
6. Persisting desire or unable to cut down on or control opioid use
7. Spending a lot of time to obtain, use, or recover from opioids
8. Continued opioid use despite persistent or recurrent social or interpersonal problems related to opioids
9. Continued use despite physical or psychological problems related to opioids
10. Failure to fulfill obligations at work, school, or home due to use
11. Activities are given up or reduced because of use

Table C-2: DSM-5 Diagnostic Criteria for Severity of OUD [197]

Severity of OUD	Number of Symptoms
Mild	Presence of 2-3 symptoms
Moderate	Presence of 4-5 symptoms
Severe	Presence of 6 or more symptoms

Appendix D: Drug Tables

A. Short-acting, Orally Administered Opioids

Table D-1: Use of Short-acting, Orally Administered Opioids in Adults [198]

Short-Acting Opioids[1]	Initial Oral Dosage (in opioid-naïve)	Additional Dosage Information	Analgesic Onset (min) Peak (min) Duration (hr)	Dosing In Special Populations	Other Considerations
Codeine (alone or in combination with APAP or ASA) ■ Codeine available as 15, 30 and 60 mg tablets ■ Combination products vary in codeine content from 15 to 60 mg/dose unit	■ 15 to 30 mg every 4 to 6 hr ■ Initial dose based upon codeine component, maximum dose based upon non-opioid component	■ Maximum APAP dose: 4000 mg/d (2000 mg/d in chronic alcoholics or in hepatic impairment) ■ Analgesic ceiling effect occurs with codeine at doses >60 mg/dose ■ Codeine alone is a weak analgesic; more effective alternatives are available (including codeine in combination with APAP or ASA)	15 to 30 30 to 60 4 to 6	■ *Elderly or debilitated*: Use with caution ■ *Hepatic dysfunction:* Conversion to active metabolite (morphine) may be reduced in patients with cirrhosis; avoid use in patients with liver disease ■ *Renal dysfunction:* Use lower dosage or an alternative analgesic	■ Codeine may be less effective in patients with decreased CYP-2D6 activity (due to poor CYP-2D6 metabolism or CYP-2D6 inhibiting drugs[2]) because of decreased conversion to the active metabolite, morphine ■ CYP-2D6 ultra-rapid metabolizers[3] can have extensive conversion to morphine with increase in opioid-mediated effects

Short-Acting Opioids[1]	Initial Oral Dosage (in opioid-naïve)	Additional Dosage Information	Analgesic Onset (min) Peak (min) Duration (hr)	Dosing In Special Populations	Other Considerations
Hydrocodone (in combination with APAP, ASA, or IBU) ■ Combination products vary in hydrocodone content (2.5 to 10 mg per dosage unit)	■ 5 to 10 mg every 6 hr (hydrocodone component) ■ Initial dose based upon hydrocodone component ■ Maximum dose based upon non-opioid component	■ Maximum dose: • 60 mg/d (4000 mg/d APAP; 2000 mg/d APAP in chronic alcoholics or hepatic impairment) for hydrocodone + APAP combination OR • 37.5 to 50 mg/d (1000 mg/d IBU) for hydrocodone + IBU combination	10 to 20 60 to 100 4 to 8	■ *Elderly or debilitated*: Use with caution; start with reduced dose (2.5-5 mg) of hydrocodone component ■ *Hepatic dysfunction:* Use with caution	■ Conversion to the active metabolite, hydromorphone, may be decreased in patients with decreased CYP-2D6 activity (due to poor CYP-2D6 metabolism or CYP-2D6 inhibiting drugs[2]) ■ CYP-2D6 ultra-rapid metabolizers[3] can have extensive conversion to hydromorphone with potential increase in opioid-mediated effects
Hydromorphone ■ Available as oral liquid 1 mg/ml, and 2, 4, and 8 mg tablets	■ 2 mg every 4 to 6 hr ■ May give an initial dose of 4 to 8 mg for severe pain	■ There is no optimal or maximum dose of hydromorphone; patients on LOT are likely to become tolerant[4] and require doses higher than the usual dosage range to maintain the desired effect	15 to 30 30 to 60 3 to 4	■ *Elderly or debilitated*: Use with caution, start at 25% to 50% of usual dose at low end of dosing range ■ *Hepatic / Renal dysfunction*: Reduce initial dose for moderate impairment, more with severe impairment	

Short-Acting Opioids[1]	Initial Oral Dosage (in opioid-naïve)	Additional Dosage Information	Analgesic Onset (min) Peak (min) Duration (hr)	Dosing In Special Populations	Other Considerations
Morphine ■ Available as oral solution (10 or 20 mg/5 ml, or 100 mg/5 ml for opioid-tolerant patients only) or as 15 or 30 mg tablets	■ 10 to 30 mg every 4 hr	■ There is no optimal or maximum dose of morphine; patients on LOT are likely to become tolerant[4] and require doses higher than the usual dosage range to maintain the desired effect	30 60 3 to 5	■ *Elderly or debilitated*: Give with extreme caution; use lower dose ■ *Hepatic dysfunction*: Use carefully in patients with cirrhosis and consider reducing dose or extending dosing interval by 1.5 to 2 times; half-life may be doubled (3 to 4 hr) and bioavailability is increased ■ *Renal dysfunction*: Reduce dose or, if severe renal impairment exists, avoid use (see *Other Considerations*)	■ M6G, an active metabolite, may accumulate in renal impairment ■ M3G, a metabolite without analgesic activity, may accumulate in renal impairment; this metabolite has been implicated in morphine-induced neurotoxicity, hyperalgesia, and allodynia

Short-Acting Opioids[1]	Initial Oral Dosage (in opioid-naïve)	Additional Dosage Information	Analgesic Onset (min) Peak (min) Duration (hr)	Dosing In Special Populations	Other Considerations
Oxycodone (alone or in combination with APAP or ASA) ■ Single-agent oxycodone available as oral solution 5 mg/5 ml, 20 mg/1 ml, and oral tablet 5, 10, 15, 20, and 30 mg ■ Combination products vary in oxycodone content, 2.5 to 10 mg per dose unit	■ 5 to 15 mg every 4 to 6 hr ■ Initial dose based upon oxycodone component ■ Maximum dose based upon non-opioid component	■ For combination products, maximum dose is limited by APAP or ASA content (4000 mg/d for both; 2000 mg/d APAP in chronic alcoholics or patients with hepatic impairment) ■ There is no optimal or maximum dose of oxycodone; patients on LOT are likely to become tolerant[4] and require doses higher than the usual dosage range to maintain the desired effect	10 to 15 30 to 60 3 to 6	■ *Elderly or debilitated*: reduce dosage ■ *Hepatic / Renal*: Use with caution; consider reducing dose and increasing frequency of dosing	■ Conversion to the active metabolite, oxymorphone, may be decreased in patients with decreased CYP-2D6 activity (due to poor CYP-2D6 metabolism or CYP-2D6 inhibiting drugs[2])

Short-Acting Opioids[1]	Initial Oral Dosage (in opioid-naïve)	Additional Dosage Information	Analgesic Onset (min) Peak (min) Duration (hr)	Dosing In Special Populations	Other Considerations
Oxymorphone ■ Available as 5 or 10 mg tablets	■ 5 mg every 4 to 6 hr	■ There is no optimal or maximum dose of oxymorphone; patients on LOT are likely to become tolerant[4] and require doses higher than the usual dosage range to maintain the desired effect	30 to 45 N/A 4	■ *Elderly or debilitated*: Use with caution and start at low end of dosing range; levels are increased 40% in patients ≥65 years ■ *Hepatic dysfunction* • *Mild hepatic impairment:* Use cautiously, start at low end of dosing range • *Moderate and severe hepatic impairment:* Contraindicated ■ *Renal dysfunction*: Bioavailability is increased 57-65% in moderate and severe impairment; start at lower doses and adjust slowly	■ Food has been shown to increase peak levels of oxymorphone immediate-release by 38%; must be taken on an empty stomach at least 1 hr before or 2 hr after a meal ■ Must NOT be taken concomitantly with alcohol; alcohol (240 ml of 4% to 40% ethanol) can cause highly variable effects on peak drug levels, ranging from a decrease of 50% to an increase of 270% (demonstrated with ER oxymorphone)

Short-Acting Opioids[1]	Initial Oral Dosage (in opioid-naïve)	Additional Dosage Information	Analgesic Onset (min) Peak (min) Duration (hr)	Dosing In Special Populations	Other Considerations
Tapentadol ▪ Available as 50, 75, or 100 mg tablets	▪ 50 mg every 4 to 6 hr	▪ Subsequent dose is 50, 75, or 100 mg every 4 to 6 hr, adjusted to analgesia and tolerability ▪ Second dose may be given 1 hr after the first dose if necessary ▪ Max recommended dose: 700 mg on first day, 600 mg on subsequent days ▪ Use tapentadol only under careful medical supervision at lowest effective dose ▪ Patients on LOT are likely to become tolerant[4] and require doses higher than the usual dosage range to maintain the desired effect	N/A (rapid) 60 4 to 6	▪ *Elderly*: Consider starting at the lowest recommended dose ▪ *Hepatic dysfunction:* • *Mild hepatic impairment:* No dosage adjustment • *Moderate hepatic impairment:* Start at 50 mg and give subsequent doses at least 8 hr apart (max. 3 doses in 24 hr) • *Severe hepatic impairment:* Use is not recommended ▪ *Renal dysfunction:* No dosage adjustment for mild or moderate renal impairment; not recommended in severe renal impairment ▪ *Respiratory dysfunction:* Use with caution because of respiratory depressant effects; consider non–mu opioid agonist analgesics	▪ Must NOT be taken concomitantly with alcohol which can increase serum tapentadol concentration ▪ If used in combination with other CNS depressants, consider dose reduction of one or both agents ▪ Use with or within 14 days of MAOIs is contraindicated

Short-Acting Opioids[1]	Initial Oral Dosage (in opioid-naïve)	Additional Dosage Information	Analgesic Onset (min) Peak (min) Duration (hr)	Dosing In Special Populations	Other Considerations
Tramadol (alone or in combination with APAP) ▪ Tramadol available as 50 mg tablet, or in tablet combination with APAP (325 mg APAP, 37.5 mg tramadol)	▪ 25 mg every morning	▪ May increase by 25 mg per day every 3 days to 100 mg tramadol/d (25 mg every 6 hr) ▪ Subsequent increments of 50 mg/d may then be made every 3 days to 200 mg/d (50 mg every 6 hr) ▪ After titration, may give 50 to 100 mg every 4 to 6 hr ▪ Maximum daily dose of tramadol: 400 mg/d ▪ Combination product: maximum 4000 mg/d APAP; 2000 mg/d APAP in chronic alcoholics or in hepatic impairment	<60 ~120 to 240 6	▪ *Elderly or debilitated:* In elderly patients >75 years: give <300 mg/d in divided dose; use with caution in debilitated patients ▪ *Hepatic dysfunction:* Decrease dosage to 50 mg once every 12 hr in patients with cirrhosis ▪ *Renal dysfunction*: • *CrCl >30 ml/min:* No change in dose or frequency required • *CrCl <30 ml/min:* Increase dosing interval to 12 hr and decrease maximum daily dose to 200 mg ▪ *Dialysis patients*: Can receive their regular dose on the day of dialysis (<7% of a dose is removed by hemodialysis)	▪ Slower initiation and titration improves tolerability ▪ Inhibits reuptake of serotonin and norepinephrine; concomitant use with MAOIs or SSRIs may increase risk of seizures, serotonin syndrome ▪ Dose carefully or use another agent in patients on serotonergic agents ▪ Seizures reported within the recommended dosage range; increased risk above recommended dosage range and in patient with seizure disorder, history of seizures, in conditions with increased risk of seizures, or with other drugs that increase seizure risk; observe maximum dose limits ▪ Serious anaphylactoid reactions reported, often following first dose; patients with a history of anaphylactoid reaction to codeine and other opioids may be at increased risk

[1] Check local formulary for available formulations.

[2] CYP-2D6 Inhibiting Drugs: Antiarrhythmics (amiodarone, propafenone, quinidine [strong inhibitor]); analgesics (methadone [weak inhibitor], propoxyphene); antihistamines (diphenhydramine, chlorpheniramine [in vitro], brompheniramine [in vitro], triprolidine [in vitro]); histamine2 receptor antagonists (cimetidine); neuroleptics (chlorpromazine, haloperidol, methotrimeprazine, perphenazine, thioridazine); protease inhibitors (ritonavir), quinine compounds (hydroxychloroquine, quinacrine, quinine); selective serotonin reuptake inhibitors (fluoxetine, fluvoxamine, paroxetine, sertraline), miscellaneous compounds (clomipramine, ketoconazole, ticlopidine)

[3] CYP-2D6 ultra-rapid metabolizers include 1% of Asian and Hispanic, 1-10% of Caucasians, 3% of African-Americans, and 16-28% of N. African and Arabic populations.

[4] Opioid tolerance is assumed in patients already taking fentanyl 25 mcg/hr OR daily doses of the following oral agents for ≥ 1 week: ≥ 60 mg oral morphine, 30 mg oxycodone, 8 mg hydromorphone, 25 mg of oxymorphone or equianalgesic dose of another opioid.

Abbreviations: APAP: acetaminophen; ASA: acetylsalicylic acid; CNS: central nervous system; CrCl: creatinine clearance; d: day(s); ER: extended-release; hr: hour(s); IBU: ibuprofen; LOT: long-term opioid therapy; M3G: morphine-3-glucuronide; M6G: morphine-6-glucuronide; MAOIs: monoamine oxidase inhibitors; mg: milligram(s); min: minute(s); mL: milliliter(s); SSRIs: selective serotonin reuptake inhibitors

B. Long-acting/Extended-release Opioids

Table D-2. Use of Long-acting/Extended-release Opioids in Adults [198]

- Long-acting/ER opioids expose patients and other users to the risks of opioid misuse and OUD, which can lead to overdose and death, even when used at recommended dosages. Long-acting/ER opioids should be reserved for patients for whom alternative analgesic treatment options (e.g., non-opioid analgesics or immediate-release opioid analgesics) are ineffective, not tolerated, or provide inadequate control of pain. Assess each patient's risk prior to prescribing long-acting/ER opioids and institute risk mitigation strategies.
- The FDA has mandated that long-acting/ER opioids be subject to a structured Risk Evaluation and Mitigation Strategy (REMS) program to manage known or potential serious risks associated with their use (see http://www.er-la-opioidrems.com/IwgUI/rems/home.action).
- Most abuse deterrent technologies have been designed to make manipulation more difficult or to make abuse of the manipulated product less attractive or less rewarding. In spite of these efforts, no opioid formulation prevents consumption of a large number of intact capsules or tablets, which continues to be the most common method of abuse.
- Long-acting/ER opioids should not be used for management of acute pain (with exception of oxycodone/acetaminophen ER tablets), as an as-needed medication, or on initiation of LOT (see Recommendation 13).

Long-Acting/ER Opioids[1]	Initial Dosage (in opioid-naïve, unless specified)	Other Dosing Information	Dosing In Special Populations	Other Considerations
Buprenorphine buccal film ▪ Available in strengths of 75, 150, 300, 450, 600, 750 and 900 mcg/film for twice daily administration	▪ 75 mcg once or twice daily for at least 4 days, then increase dose to 150 mcg every 12 hr ▪ There is potential for buprenorphine to precipitate withdrawal in patients already on opioids; to reduce risk, the dose of other opioid should be tapered to ≤30 mg MEDD before initiating buprenorphine	▪ After initial dosing, dosing changes as necessary can proceed in increments of 150 mcg every 12 hr, no more frequently than every 4 days ▪ Patients on prior dose of opioid 30 to 89 mg MEDD may initiate buprenorphine film at 150 mcg every 12 hr, 90 to 160 mg MEDD may initiate at 300 mcg every 12 hr; if prior opioid is >160 mg MEDD – consider an alternative analgesic ▪ Time to steady state ~3 days with every 12 hr dosing	▪ *Elderly:* Initiation at the low end of the dosing range is recommended ▪ *Renal dysfunction:* No dose adjustment recommended ▪ *Hepatic dysfunction:* Patients with severe hepatic impairment should have starting and titration doses reduced by half that of patients with normal liver function	▪ QTc prolongation reported with recommended doses of buprenorphine; maximum dose of 900 mcg every 12 hr established due to the potential for this adverse effect; avoid in patients with Long QT Syndrome, family history of Long QT Syndrome, or those taking Class IA or Class III antiarrhythmic drugs ▪ Buprenorphine buccal film is a potential treatment option for patients with significant renal impairment and those with gastrointestinal structural or functional abnormality that interferes with swallowing or absorption of orally administered medications
Buprenorphine TDS ▪ Available in every 7 day patch formulation that delivers transdermal buprenorphine at the following rates: 5 mcg/hr, 7.5 mcg/hr, 10 mcg/hr, 15 mcg/hr, and 20 mcg/hr	▪ In opioid-naïve or in patients on <30 mg MEDD of alternate agent: Initiate treatment with 5 mcg/hr patch ▪ There is potential for buprenorphine to precipitate withdrawal in patients already on opioids; to reduce risk, the dose of other opioid should be tapered to ≤30 mg MEDD before initiating buprenorphine; the 10 mcg/hr patch may then be initiated at the next dosing interval	▪ The maximum dose of buprenorphine TDS 20 mcg/hr may not provide adequate analgesia for patients requiring greater than 80 mg MEDD; an alternate analgesic should be considered ▪ Steady state achieved in ~3 days	▪ Dosage does not need to be adjusted in patients with mild or moderate hepatic impairment, renal impairment, or in the elderly ▪ Potential treatment option for patients with significant renal impairment or those with gastrointestinal structural or functional abnormality that interferes with swallowing or absorption of oral medications	▪ Buprenorphine patch 10 mcg/hr is approximately equivalent to an oral MEDD of 18-28 mg; the 20 mcg/hr patch is approximately equivalent to a MEDD of 36-55 mg ▪ Dose of one 20 mcg/hr patch per week should not be exceeded due to risk of QTc prolongation ▪ Avoid use in patients with Long QT Syndrome, family history of Long QT Syndrome, or those taking Class IA or Class III antiarrhythmic medications ▪ Advise patients that application of external heat (e.g., hot baths, sunbathing, saunas, heating pads) increases maximum plasma concentration of buprenorphine and risk of fatal overdose

Long-Acting/ER Opioids[1]	Initial Dosage (in opioid-naïve, unless specified)	Other Dosing Information	Dosing In Special Populations	Other Considerations
Fentanyl TDS ■ Available in every 3 day patch formulation that delivers transdermal fentanyl at the following rates: 12 mcg/hr, 25 mcg/hr, 50 mcg/hr, 75 mcg/hr, and 100 mcg/hr	■ Fentanyl TDS is contraindicated in non-opioid-tolerant patients ■ Fentanyl TDS is contraindicated in the management of mild or post-operative pain, and as an "as-needed" analgesic ■ The initial dose of fentanyl TDS in opioid-tolerant patients [2] is 25 mcg/hr, applied every 72 hr; the 12 mcg/hr dose has not been evaluated as an initial dose	■ Fentanyl TDS must be used only on intact skin ■ Dose change increments should be based on supplemental opioid doses, using a ratio of fentanyl TDS 12 mcg/hr for every 45 mg/24 hr of supplemental oral MEDD ■ Dosing changes, as necessary, should occur at least 3 days after the initial dose; thereafter, not more often than every 6 days	■ *Elderly:* Twice as sensitive to fentanyl as younger patients; avoid initiation at doses >25 mcg/hr unless patient is already taking >135 mg oral morphine or equivalent ■ *Hepatic / Renal dysfunction:* Reduce dose by 50% in mild-moderate impairment and avoid use if impairment is severe ■ *Patients with fever*: Increased body temperature may increase release of fentanyl from the TDS; monitor patients for opioid adverse effects and modify dosage as necessary	■ Consider fentanyl TDS in patients with persistent, moderate-to-severe pain who cannot take oral ER morphine or oral ER oxycodone ■ Avoid application of external heat sources (e.g., heating pads, electric blankets, heat lamps, saunas, hot tubs, hot baths, sunbathing, heated water beds) to the application site while the patch is worn as heat may increase release and speed absorption of fentanyl ■ Using damaged or cut fentanyl TDS patches can lead to rapid release of the contents of the patch and fatal overdose ■ Use of fentanyl TDS with CYP3A4 inhibitors[3] can result in increased fentanyl plasma concentrations, increased or prolonged opioid effects, including fatal respiratory depression; use extreme caution and frequent monitoring in patients receiving these combinations ■ CYP 3A4 inducers may increase fentanyl clearance

Long-Acting/ER Opioids[1]	Initial Dosage (in opioid-naïve, unless specified)	Other Dosing Information	Dosing In Special Populations	Other Considerations
Hydrocodone ER ■ **ER tablets** contain 20, 30, 40, 60, 80, 100 or 120 mg hydrocodone for once daily administration ■ **ER capsules** contain 10, 15, 20, 30, 40 or 50 mg hydrocodone for every 12 hr administration	■ *Opioid-naïve patients:* 20 mg ER tablet once daily ■ *Opioid-naïve patients:* 10 mg ER capsule every 12 hr ■ *Opioid tolerant [2] patients:* Convert current opioid to equianalgesic daily dose of hydromorphone ER; reduce the calculated amount by 33-50% for initial start dose (see Table D-3)	■ *For opioid-experienced, both ER tablets and capsules:* Convert current opioid to equianalgesic hydrocodone dose then reduce that dose by 25%; initiate at nearest whole-tablet or capsule strength, rounding down as necessary ■ *For both tablets and capsules:* Dose change increments of 20 mg per day may be made every 3 to 7 days ■ Steady state achieved in ~3 days of dosing	■ *Elderly:* No significant pharmacokinetic differences ■ *Patients with renal impairment:* Hydrocodone plasma concentrations are increased in moderate or severe impairment; use low initial dose and monitor closely for adverse events such as excessive sedation and respiratory depression ■ *Patients with hepatic impairment:* no dosage adjustment is required in mild or moderate hepatic impairment; start with the lowest dose, 10 mg, in patients with severe hepatic impairment, and monitor closely	■ CYP3A4 inhibitors[3] may decrease clearance of hydrocodone, increase plasma concentrations, and increase risk of overdose; CYP3A4 inducers[4] may increase clearance and reduce opioid effect ■ Both ER tablets and ER capsules are formulated with polyethylene oxide which imparts ER properties ■ Hydrocodone ER tablets or capsules must be swallowed intact and should not be cut, broken, chewed, crushed or dissolved due to risk of fatal overdose ■ ER tablet has abuse deterrent labeling related to resistance to crushing and high viscosity when dissolved in aqueous solution ■ ER capsule has abuse deterrent properties but is not FDA-labeled as an abuse deterrent formulation

Long-Acting/ER Opioids[1]	Initial Dosage (in opioid-naïve, unless specified)	Other Dosing Information	Dosing In Special Populations	Other Considerations
Hydromorphone ER Tablets ■ Available as 8, 12, 16, and 32 mg tablets for once daily administration	■ Not indicated in opioid-naïve patients due to the risk of respiratory depression ■ *Opioid tolerant[2] patients:* Convert current opioid to equianalgesic daily dose of hydromorphone ER; reduce the calculated amount by 33-50% for initial start dose (see Table D-3)	■ Dosage adjustments may be made in increments of 4 to 8 mg every 3 to 4 days as needed to achieve adequate analgesia ■ Steady state reached after 3 to 4 days of once-daily dosing	■ *Elderly:* No specific guidance; monitor closely, particularly when initiating or titrating dosage ■ *Patients with renal impairment:* Start patients with moderate impairment at 50% of usual dose, and patients with severe impairment at 25% of usual dose ■ *Patients with hepatic impairment:* Start patients with moderate impairment at 25% of usual dose in non-impaired patients	■ Hydromorphone ER tablets must be swallowed intact and should not be cut, broken, chewed, crushed or dissolved due to risk of fatal overdose ■ Hydromorphone ER contains sulfites ■ Hydromorphone ER has abuse deterrent properties but is not FDA-labeled as an abuse deterrent formulation

Long-Acting/ER Opioids[1]	Initial Dosage (in opioid-naïve, unless specified)	Other Dosing Information	Dosing In Special Populations	Other Considerations
Methadone ▪ Available as 5 and 10 mg tablets and oral solution, 5 or 10 mg/5 ml, for every 8 to 12 hr administration	▪ Should not be used for as-needed supplemental OT ▪ *Initial dose:* 2.5 to 5 mg orally every 8 to 12 hr; more frequent administration (every 6 hr) may be necessary during initiation to maintain analgesia ▪ START LOW AND GO SLOW ▪ See Appendix D for detailed dosing information including dosing recommendations in patients previously exposed to opioids ▪ Monitor patients carefully during initiation, conversions to and from other opioids, and dose titration	▪ Dose change increments of ▪ 2.5 mg every 8 hr may be made every 5 to 7 days ▪ Delayed analgesia or toxicity may occur because of drug accumulation after repeated doses, e.g., on days 2 to 5; if patient has excessive sedation during this timeframe, consider temporarily holding dose(s), lowering the dose, and/or slowing the titration rate ▪ Once a stable analgesic dose is reached, the dosing interval may be extended to every 8 to 12 hr or longer	▪ *Elderly or debilitated*: Consider reduced dosing in elderly or debilitated patients who may be more sensitive to opioid adverse effects ▪ *Hepatic dysfunction*: No dosage adjustments required in patients with stable chronic liver disease or mild-to-moderate hepatic dysfunction; avoid in severe liver disease ▪ *Renal dysfunction*: Methadone and its metabolites do not accumulate in patients with renal failure; however, dosage reduction by up to 50-75% is recommended in patients with CrCl <10 mL/min	▪ Prescribers of methadone should be thoroughly familiar with its complex pharmacokinetic and pharmacodynamic properties or consult a clinician with experience in dosing methadone ▪ Plasma half-life (22 to 128 hr short-term; 24 to 48 hr at steady-state) may be longer than the analgesic duration ▪ Methadone has little cross-tolerance with other opioids; therefore, even patients with a high degree of opioid tolerance may be at risk for overdose when switched to methadone ▪ Methadone is the only long-acting opioid available as an oral solution ▪ Methadone may be subject to drug interactions with agents that can influence CYP2B6 (e.g., ticlopidine) ▪ May prolong QTc intervals on ECG; risk of torsade de pointes; see Appendix D for detailed QTc monitoring information

Long-Acting/ER Opioids[1]	Initial Dosage (in opioid-naïve, unless specified)	Other Dosing Information	Dosing In Special Populations	Other Considerations
Morphine CR or SR ▪ Available in 15, 30, 60, 100, and 200 mg strengths for every 8 to 12 hr administration ▪ Morphine ER capsules available in 10, 20, 30, 40, 50, 60, 70, 80, 100, 130, 150, and 200 mg capsule strengths for once daily administration **Morphine and Naltrexone ER Capsule** ▪ Available as 20/0.8, 30/1.2, 50/2, 60/2.4, 80/3.2, and 100/4 capsule strengths (mg morphine/mg naltrexone) for once or twice-daily administration	▪ *Opioid-naïve patients:* Morphine CR or SR 15 mg every 8 to 12 hr ▪ Total daily increments of <30 to 40 mg/d may be made every 2 days ▪ *Opioid-naïve patients:* Morphine ER capsules are not indicated in opioid-naïve patients ▪ *Patients who are not opioid tolerant:* Start morphine ER at 30 mg daily, may adjust every 1 to 2 days ▪ *Opioid-naïve patients:* Initiate at the lowest dose, 20 mg/0.8 mg once daily ▪ *Opioid tolerant*[2] *patients:* Convert current opioid to equianalgesic daily dose of morphine; reduce the calculated amount by 33-50% for initial start dose (see Table D-3) ▪ Dose may be up titrated no more frequent than every other day	▪ Morphine CR or SR tablets should be swallowed whole, not broken, chewed, or crushed ▪ For patients who have difficulty swallowing, SR and ER capsules may be opened and the pellets may be sprinkled onto a small amount of soft food (for administration without chewing) or administered via 16F gastrostomy tube ▪ Steady state achieved with morphine ER within 24 to 36 hr ▪ Morphine/naltrexone must be swallowed whole or the contents of the capsules sprinkled on apple sauce; crushing, dissolving, or chewing pellets may cause a fatal overdose (particularly in the opioid-naïve patient) and the absorption of naltrexone could increase the risk of precipitating withdrawal in opioid tolerant patients ▪ Morphine/naltrexone: If once daily administration results in inadequate analgesia, may switch to twice daily dosing	*Information applies to all formulations of morphine listed* ▪ *Elderly:* Use with caution and at lower dose ▪ *Patients with renal dysfunction:* Bioavailability is increased and clearance is decreased; metabolites M3G and M6G accumulate significantly ▪ Reduce dose or, if severe renal impairment exists, avoid use ▪ *Patients with hepatic dysfunction:* Clearance decreases and half-life increases; M3G and M6G to morphine ratios are reduced; use carefully in patients with cirrhosis and consider reducing dose or extending dosing interval by 1.5 to 2 times	▪ Morphine SR is preferred first-line long-acting agent because of similar efficacy to other long-acting opioids, comparable safety profile, provider familiarity with use, and lower cost ▪ M6G, an active metabolite, may accumulate in renal impairment and contribute to excessive opioid effects ▪ M3G, a metabolite without analgesic activity, may accumulate in renal impairment; this metabolite has been implicated in morphine-induced neurotoxicity, hyperalgesia, and allodynia ▪ Morphine/naltrexone ER capsule has abuse deterrent labeling related to potential to precipitate withdrawal if drug is taken by other than oral route

Long-Acting/ER Opioids[1]	Initial Dosage (in opioid-naïve, unless specified)	Other Dosing Information	Dosing In Special Populations	Other Considerations
Oxycodone ER ■ **Tablets** available in 10, 15, 20, 30, 40, 60, and 80 mg strengths for every 12 hr administration ■ **Capsules** available in 9, 13.5, 18, 27 and 36 mg strengths for every 12 hr administration	■ *Opioid-naïve patients:* 10 mg (tablets) or 9 mg (capsules) orally every 12 hr ■ *Opioid tolerant[2] patients:* Convert current opioid to equianalgesic daily dose of oxycodone ER; reduce the calculated amount by 33-50% for initial start dose (see Table D-3)	■ *Dose change increments:* May increase to 20 mg (tablets) or 18 mg (capsules) every 12 hr after 1 or 2 days; thereafter, the total daily dose may be increased by 25-50% of the current dose every 1 or 2 days ■ ER tablets are not bioequivalent to ER capsules; 10 mg oxycodone HCl (ER tablet) = 9 mg oxycodone base (ER capsule) ■ Steady state achieved with tablets or capsules in 24 to 36 hr with repeat dosing	■ *Elderly*: Plasma concentrations of oxycodone are increased ~15% in the elderly; however, usual dosing and dosing intervals may be appropriate ■ *Patients with renal dysfunction*: Plasma concentrations of oxycodone are increased ~50% in patients with CrCl <60 ml/min; dose conservatively and adjust according to clinical situation ■ *Patients with hepatic dysfunction*: Reduce initial dose to 1/3 to 1/2 of the usual dose and monitor closely	■ Recommended for patients who experience intolerable, unmanageable adverse effects to long- acting morphine ■ Both ER tablets and ER capsules have abuse deterrent labeling related to resistance to abuse by intranasal and intravenous means ■ ER tablets should be swallowed whole, not broken, chewed, or crushed ■ ER capsules may be opened and sprinkled on soft food or administered via feeding tube

Long-Acting/ER Opioids[1]	Initial Dosage (in opioid-naïve, unless specified)	Other Dosing Information	Dosing In Special Populations	Other Considerations
Oxycodone/APAP ER ■ Available as tablets containing oxycodone 7.5 mg and APAP 325 mg for every 12 hr administration	■ *Opioid-naïve patients:* May initiate therapy with the standard dose of 2 tablets every 12 hr ■ A standard, single dose consists of 2 tablets totaling 15 mg oxycodone/650 mg APAP ■ This is the only long-acting/ER opioid to have an acute pain indication	■ The polyethylene oxide content causes the tablet to swell and become sticky when wet. This has the potential to cause obstruction of the airway or GI obstruction ■ Steady state concentration of both components are reached within 24 hr of product initiation	■ *Elderly:* Take precautions when determining the dosing amount and frequency in geriatric patients since a greater sensitivity to oxycodone may be observed in this patient population when compared to younger patients ■ *Patients with renal or hepatic dysfunction:* Patients with renal dysfunction (CrCl <60 ml/min) or hepatic dysfunction should initiate therapy with 1 tablet every 12 hr and adjust as needed	■ This long-acting/ER opioid is an exception to the REMS requirements due to the relatively low amount of oxycodone contained in each tablet ■ Oxycodone/APAP ER tablets are formulated with PEO which is responsible for its ER in addition to labeled abuse deterrent properties ■ Patients should be instructed not to pre-soak, lick, or otherwise wet tablets prior to swallowing and to take one tablet at a time with adequate water to insure complete and immediate swallowing

Long-Acting/ER Opioids[1]	Initial Dosage (in opioid-naïve, unless specified)	Other Dosing Information	Dosing In Special Populations	Other Considerations
Oxymorphone ER Tablets ■ Available as 5, 7.5, 10, 15, 20, 30 and 40 mg tablets for every 12 hr administration	■ *Opioid-naïve patients:* Initiate at 5 mg every 12 hr ■ *Opioid tolerant[2] patients:* Convert current opioid to equianalgesic daily dose of oxycodone; reduce the calculated amount by 33-50% for initial daily start dose (see Table D-3)	■ *Dose change increments:* May increase by 5 to 10 mg every 12 hr every 3 to 7 days ■ Oxymorphone ER tablets must be taken whole, one tablet at a time, with enough water to ensure complete swallowing immediately after placing in the mouth ■ Steady-state plasma levels are achieved after 3 days of multiple dose administration	■ *Elderly:* Plasma drug levels are about 40% higher in elderly versus younger subjects; use caution, starting at the low end of dosing range and titrating slowly ■ *Patients with renal dysfunction:* Bioavailability is increased by 57% in moderate impairment and by 65% in severe impairment; in patients with CrCl <50 mL/min, oxymorphone should be started with the lowest dose and titrated slowly ■ *Patients with hepatic dysfunction:* Use with caution in patients with mild hepatic impairment, starting with lowest dose and titrating slowly ■ Contraindicated in patients with moderate or severe hepatic impairment	■ Must be taken on an empty stomach at least 1 hr before or 2 hr after a meal; food has been shown to increase peak levels of oxymorphone ER by 50% ■ Must NOT be taken concomitantly with alcohol, which can cause highly variable effects on peak drug levels, ranging from a decrease of 50% to an increase of 270%

Long-Acting/ER Opioids[1]	Initial Dosage (in opioid-naïve, unless specified)	Other Dosing Information	Dosing In Special Populations	Other Considerations
Tapentadol ER ▪ Available as tablets containing 50, 100, 150, 200, or 250 mg tapentadol for twice daily dosing	▪ *In opioid-naïve and non-tolerant patients:* Initiate therapy with 50 mg twice daily; use of higher starting doses in patients who are not opioid tolerant may cause fatal respiratory depression ▪ There are no established conversion ratios for conversion from other opioid to tapentadol ER; convert current opioid to an estimated equianalgesic daily dose of tapentadol; reduce the calculated amount by 33-50% for initial daily start dose (see Table D-3)	▪ *Dose change increments:* May increase dose by no more than 50 mg twice daily every 3 days ▪ *Maximum daily dose*: 500 mg daily ▪ Tapentadol ER tablets must be taken whole; crushing, chewing, or dissolving tablets will result in uncontrolled delivery of tapentadol and can lead to overdose or death ▪ Steady state is attained after the third dose (24 hr after the first twice daily multiple dose administration)	▪ *Elderly:* No dosing adjustment needed, consider starting at lowest recommended dosage ▪ *Patients with renal dysfunction:* No dosage adjustment for mild or moderate renal impairment; not recommended in severe renal impairment ▪ *Patients with hepatic dysfunction:* Use not recommended in severe hepatic impairment	▪ Must NOT be taken concomitantly with alcohol which can increase serum tapentadol concentration and cause fatal overdose ▪ Use with or within 14 days of MAOIs is contraindicated
Tramadol ER ▪ Available as 100, 200 and 300 mg tablets for once daily administration	▪ *Patients not currently on tramadol:* 100 mg once daily ▪ Converting from tramadol IR: Start at 24 hr dosage equivalent rounded down to closest 100 mg increment	▪ *Dose change increments:* May increase by 100 mg every 5 days based on analgesia and tolerability ▪ Maximum dose: 300 mg/day	▪ *Elderly:* Start at low end of dosing range; use particular caution, especially in patients >75 years ▪ *Renal dysfunction:* Avoid use if CrCl <30 ml/min ▪ *Hepatic dysfunction:* Avoid use in severe hepatic impairment (Child- Pugh Class C)	▪ Must be swallowed whole and must not be chewed, crushed, or split ▪ See warnings and precautions under Other Considerations for tramadol IR (Table D-1)

[1]Check local formulary for available formulations.

[2] Opioid tolerance is assumed in patients already taking fentanyl 25 mcg/hr OR daily doses of the following oral agents for ≥ 1 week: ≥ 60 mg oral morphine, 30 mg oxycodone, 8 mg hydromorphone, 25 mg of oxymorphone or equianalgesic dose of another opioid.

[3]CYP3A4 inhibiting agents include: ritonavir, ketoconazole, itraconazole, troleandomycin, clarithromycin, nelfinavir, nefazodone, amiodarone, amprenavir, aprepitant, diltiazem, erythromycin, fluconazole, fosamprenavir, grapefruit juice, verapamil

[4] CYP3A4 inducing agents include: carbamazepine, phenobarbital, phenytoin, primidone, rifampin

Abbreviations: APAP: acetaminophen; CR: morphine controlled; CrCl: creatinine clearance; CYP2B6: cytochrome P450 2B6; CYP3A4: cytochrome P450 3A4; ECG: electrocardiogram; ER: extended-release; GI: gastrointestinal; HCl: hydrochloride; hr: hour(s); IR: immediate release; M3G: morphine-3-glucuronide; M6G: morphine-6-glucuronide; MAOIs: monoamine oxidase inhibitors; mcg: microgram(s); MEDD: morphine equivalent daily dose; mg: milligram(s); min: minute(s); mL: milliliter(s); OT: opioid therapy; PEO: polyethylene oxide; TDS: transdermal system; QTc: the heart rate's corrected time interval from the start of the Q wave to the end of the T wave; REMS: Risk Evaluation and Mitigation Strategy; SR: sustained release

C. Morphine Milligram Equivalent Doses

Table D-3: Morphine Milligram Equivalent Doses for Commonly Prescribed Opioids[33]

Morphine Milligram Equivalent Doses (MME)		
Opioid Agent	**Conversion Factor**	■ All doses in mg/d except for fentanyl. ■ Multiply the daily dosage for each opioid by the conversion factor to determine the equianalgesic dose in MME. Equianalgesic dose conversions are only estimates and cannot account for individual variability in genetics and pharmacokinetics. ■ Do not use the calculated dose in MME to determine the doses to use when converting one opioid to another. When converting opioids, the new opioid is typically dosed at substantially lower than the calculated MME dose (33-50% less) to avoid accidental overdose due to incomplete cross-tolerance and individual variability in opioid pharmacokinetics. ■ Use particular caution with fentanyl because it is dosed in mcg/hr instead of mg/d, and absorption is affected by heat and other factors. ■ See Table D-2 for conversion guidance for buprenorphine-containing agents.
Codeine[1]	0.15	
Tapentadol[2]	0.4	
Morphine	1	
Hydrocodone	1	
Oxycodone	1.5	
Oxymorphone	3	
Hydromorphone	4	

[1]When converting from weak opioid analgesics to more potent opioids, use the recommended initial doses of the new opioid for opioid-naïve patients.

[2]The conversion factor estimate for tapentadol is based upon μ-receptor agonist activity in animal models where tapentadol has been shown to be 2-3 times less potent than morphine.

Abbreviations: d: day(s); hr: hour(s); mcg: microgram(s); mg: milligrams; MME: morphine milligram equivalent dose

D. Methadone Dosing Guidance

a. Summary

- Methadone is not a first-line agent for the treatment of chronic pain.[33] It is an alternative long-acting opioid analgesic that may be useful in managing pain severe enough to require continuous daily treatment for which alternative treatment options are inadequate.
- In general, as with other opioids, methadone should be used as one aspect of a comprehensive pain management plan, as agreed upon by the practitioner and the patient.
- Methadone should be initiated and adjusted by, or in consultation with, a practitioner who has the relevant knowledge and expertise;[33] if a provider with clinical experience is not available, then another long-acting opioid may be used until such consultation is obtained.
- The general principles utilized in the dosing of methadone are different than those of other opioids; these differences are due to methadone's unique pharmacokinetic and pharmacodynamic properties and include, but are not limited to:
  - Dose titration should occur after at least 5-7 days on a designated dose (in the large majority of cases)
  - Careful consideration must be given to potential drug interactions and to the potential for QT prolongation
- Methadone is considered to be safe in patients with renal and/or hepatic impairment but should be used with caution in end-stage disease cases of these conditions.
- There are a number of methods available that use conversion ratios to initiate or titrate methadone; no single method is considered superior to others. Titration should be based on patient response and not solely based on equianalgesic dosing tables.
- Monitoring ECG for QTc interval prolongation is recommended based upon certain clinical scenarios.

b. Overview

Methadone is indicated for persistent, moderate-to-severe chronic pain in patients requiring continuous, around-the-clock opioid administration over an extended time. Methadone's pharmacokinetic properties are complex and incompletely documented.[199,200] It has a long elimination half-life that has wide inter-patient variability (mean or median half-life, depending on subject type, ranges from 3-128 hr) [201-214] and does not reflect duration of analgesia.[210,215] Initially, methadone duration of analgesia ranges from 4-6 hr; however, with repeated dosing, duration of analgesia can extend to 8-12 hr. Accordingly, while initial dosing may require more frequent administration (three times per day [TID]) to achieve adequate analgesia,[216,217] once steady-state levels are established, reducing dosing frequency to two times per day (BID) can be considered. In elderly and frail patients, consideration may be given to starting with BID dosing. Also, as a result of the dissociation between half-life and analgesic duration, tissue accumulation of methadone can occur. It may take ten days for plasma levels to stabilize; thus, as a general rule, dose titration should not be more frequent than every 5-7 days.[218] Patients should be reassessed more frequently (e.g., every few days) when methadone is initiated and when the dose is increased.[33] Once stable dosing is established, follow-up can be as clinically warranted.

While methadone is an alternative to ER morphine or oxycodone for treatment of moderate-to-severe pain, a number of authors have cautioned about the complexities of dosing and suggested the drug be prescribed by practitioners with relevant experience, in an adequately monitored setting.[33,216,217,219-225] Significant toxicity has occurred particularly when doses were increased too frequently, conversion doses were too high, or dosing intervals too close.[222,226-228]

In 2014, a methadone safety guideline was developed by the American Pain Society and College of Problems of Drug Dependence, in collaboration with the Heart Rhythm Society, which made recommendations for safer prescribing of methadone.[169] Table D-4 outlines baseline and monitoring recommendations based on categorization of patients for risk of QTc prolongation. Palliative care patients with the goal of comfort care may require less vigilance with ECG monitoring.

Table D-4: Baseline and Monitoring Recommendations Based on Categorization of Patients for Risk of QTc Prolongation [169]

Category	Baseline ECG	Follow Up ECGs[1]	Action
Patients with risk factors for QTc prolongation, any prior QTc >450, or history of syncope	Obtain baseline ■ ECG within last 3 months is sufficient ■ Strong recommendation ■ Low quality evidence	■ 2-4 weeks after initiation ■ With significant dose increases ■ When methadone dose reaches 30-40[2] mg/d ■ When methadone dose reaches 100 mg/d[2] ■ When new risk factors arise or signs or symptoms of suggestive arrhythmia	■ Avoid use if QTc >500 ms[3] ■ Consider alternative to methadone for QTc 450-500[3] ■ Evaluate and correct reversible causes of QTc prolongation
Patients not known to be at higher risk of QTc prolongation	Consider baseline ■ ECG within the last 12 months is sufficient ■ Weak recommendation ■ Low quality evidence	■ When methadone dose reaches 30-40[2] mg/d ■ When dose reaches 100 mg/d[2] ■ When new risk factors arise or signs or symptoms of suggestive arrhythmia	■ Avoid use if QTc >500 ms[3] ■ Consider alternative to methadone for QTc 450-500[3] ■ Evaluate and correct reversible causes of QTc prolongation

[1]Consider obtaining yearly ECGs once a stable dose is reached.

[2]Doses this high are not recommended for chronic pain and are typically observed only for patients receiving methadone for MAT for OUD.

[3]For patients on stable doses of methadone in whom a prolonged QTc has been noted (QTc >450 ms), consider tapering the dose of methadone and repeating the ECG. Other QT prolonging medications should be evaluated and cardiology specialty care should be consulted for expert opinion.

Abbreviations: d: day(s); ECG: electrocardiogram; MAT: medication assisted treatment; ms: millisecond(s); mg: milligram(s); OUD: opioid use disorder; QTc: QTc interval (the heart rate's corrected time interval from the start of the Q wave to the end of the T wave)

Special caution is recommended with concurrent benzodiazepines and drugs that prolong the QT interval.[229]

Methadone is primarily metabolized by CYP450 2B6 to inactive/nontoxic metabolites.[230-236] CYP2B6 is a highly polymorphic gene[237] and may help to explain why the pharmacokinetics of methadone can be extremely variable from individual to individual. Currently, it is unclear whether cytochrome P450 3A has

any influence on methadone metabolism and caution is encouraged when using drugs that interact with both enzymes.

c. Dosing Strategies

The dosing recommendations listed below (in Table D-5) are provided to offer guidance on using methadone in the treatment of patients with chronic pain, particularly when converting from another opioid to methadone. The use of methadone for pain should be done in the context of a pain clinic or with assistance of local pain management experts, including healthcare providers or pharmacists, who have experience with methadone's use. If such resources are not readily available, other long-acting opioids should be considered (e.g., morphine sustained action [SA], or oxycodone SA).

Various methadone dosing strategies have been employed [224,238,239] and methods are still evolving. Older, prospective studies found no evidence to support the superiority of one dosing strategy over another.[220,240,241] The lack of prospective and comparative studies concerning methadone dosing strategies highlights the need to carefully individualize the dosing regimen of methadone.

For opioid tolerant patients, a number of different equianalgesic dose ratio tables can be used to determine the dose of methadone.[220,223,242-245] This VA/DoD OT CPG includes one of the more conservative equianalgesic dose ratio tables as a reference for providers to discuss and/or consider (Table D-3).[245] Local subject matter experts may prefer, or be more familiar with, other accepted (evidence-based) equianalgesic dose ratio tables. No equianalgesic dose ratio table is considered superior and all have similar limitations. When converting to methadone, lower MEDDs have lower conversion ratios than higher MEDDs. As compared to lower MEDDs, higher MEDDs may convert to smaller methadone doses than one might expect. For example, 60 mg MEDD would be ~15 mg of methadone/day (a ratio of ~4:1); whereas 180 mg MEDD would be ~22.5 mg/day (a ratio of ~8:1). Methadone dose conversion is not a linear process. Furthermore, while the equianalgesic dose ratio tables account for cross-tolerance,[218] some subject matter experts feel the calculated methadone dose should be further decreased for incomplete cross-tolerance, especially for patients on higher MEDDs. [169,246]

Table D-5: Dosing Recommendations for Patients Receiving Codeine Preparations or No Previous Opioids [247,248]

Dosing Strategy	Initial Methadone Dose	Increments	Comments
Gradual titration (For CNCP and situations necessitating less frequent monitoring)	2.5 mg every 12 hr or 8 hr	2.5 mg every 12 hr or 8 hr, no more often than every 5 to 7 d	As a general rule, *start low and go slow*
Faster titration (For cancer pain and situations where frequent monitoring is possible)	2.5-5 mg every 8 hr	2.5 to 5 mg every 8 hr as often as every third day	

Note: All doses refer to oral administration
Abbreviations: CNCP: chronic non-cancer pain; d: day(s); hr: hour(s); mg: milligram(s)

Table D-6: Equianalgesic Dose Ratios [245,246]

Morphine Dose (mg/d)	<30	31-99	100-299	300-499	500-999	1000-1200	>1200
Morphine: Methadone	2:1	4:1	8:1	12:1	15:1	20:1	Consult

Note: The conversion ratio increases as the morphine equivalent dose increases [33,220-222,249]
Abbreviations: d: day(s); mg: milligram(s)

The equianalgesic dose ratio is only one component of the process for appropriate dosing of methadone and other opioids. Once the dose is determined, there are two different methods to make the switch: a rapid conversion method and a stepwise/phased conversion. Again, no one conversion method has been determined to be superior to the others.

- For rapid conversion, the previous opioid is discontinued and the calculated methadone dose is started on day one.
- For the stepwise/phased conversion, the dose of the previous opioid is decreased by 1/3 and replaced with 1/3 of the calculated methadone dose (given in three divided doses). Then the previous opioid dose is decreased by an additional 1/3 and the methadone dose is increased by 1/3. Finally, the remaining 1/3 of the previous opioid dose is discontinued and the methadone dose is increased to the initial calculated dose. This can be done over several days or weeks.[218,250]

For breakthrough pain, a short-acting opioid preparation (e.g., acetaminophen with hydrocodone, oxycodone with or without acetaminophen, or immediate-release morphine) may be used until steady state is achieved (i.e., 5-7 days). As-needed methadone has also been used in a palliative care setting;[224,238,240] however, it is generally discouraged to avoid drug accumulation. It is important to note that use of breakthrough pain medications in patients with CNCP is controversial. If opioid medications for breakthrough pain are indicated, following titration to a stable methadone dose in CNCP patients, they should be used sparingly.[241]

d. Converting from Methadone to Oral Morphine

Switching from methadone to another opioid is not simply the reverse process; the equianalgesic dose ratio tables previously mentioned are not bi-directional and cannot be used in reverse (i.e., the morphine to methadone conversion ratio may not be the same as the methadone to morphine ratio).[251] There is no widely accepted conversion strategy for switching from methadone to another opioid. A proposed safe and conservative approach is a 1:3 methadone to morphine ratio (10 mg methadone/day = 30 mg oral morphine/day).[218] However, literature suggests patients may end up on as high as 1:4.7 methadone to morphine ratio (10 mg methadone = 47 mg morphine).[252]

e. Special Patient Populations

Patients 65 years and older may have decreased clearance of methadone.[212] Dosage adjustments do not appear necessary in patients with stable chronic liver disease; in addition, methadone and its metabolites do not accumulate in patients with renal failure.[253] However, two prospective studies on methadone dosing strategies excluded patients with liver or renal disease,[220,240] thus caution should

be observed when dosing methadone in these populations. Dosage adjustments may be necessary in patients with end-stage liver or renal disease.

f. Patient Education

Discuss the following information with patients prior to and during treatment with methadone:[243]

- Methadone must be taken only as directed. Patients should never take extra doses without getting approval from the prescriber.
- Taking methadone as frequently as other opioids may produce a fatal overdose.
- Patients should use other CNS depressants (especially benzodiazepines) with caution and only as directed by a healthcare provider.
- Patients should only use methadone in combination with other opioids as prescribed by a healthcare provider.
- The use of illicit drugs and/or alcohol with methadone may be fatal.
- Pain relief builds gradually and usually takes 5-7 days to see the full effects of a particular dose.
- Patients should tell all medical providers that they are taking methadone. Adding medications or changing dosing of other medications can affect methadone and should be coordinated with the methadone prescriber.
- Patients should avoid activities requiring mental alertness or coordination (such as driving or using machinery) until the effects of methadone are realized, typically a week or longer.
- Patients should rise slowly from a sitting/supine position, as methadone may cause dizziness.
- Methadone, like other opioids, can cause significant constipation. Patients should take a prescribed laxative as directed.
- Patients should report any of the following symptoms immediately and/or seek urgent/emergent care: dizziness or lightheadedness, irregular heartbeat (palpitations), falls or near falls, chest pain/pressure, and shortness of breath.
- Patients should avoid abrupt discontinuation of methadone without first consulting a healthcare provider.

Appendix E: Evidence Review Methodology

A. Developing the Scope and Key Questions

The CPG Champions, along with the Work Group, were tasked with identifying KQs to guide the systematic review of the literature on LOT. These questions, which were developed in consultation with the Lewin Team, addressed clinical topics of the highest priority for the VA and DoD populations. The KQs follow the population, intervention, comparison, outcome, timing, and setting (PICOTS) framework for evidence questions, as established by the Agency for Healthcare Research and Quality (AHRQ). Table E-1 provides a brief overview of the PICOTS typology.

Table E-1. PICOTS [254]

P	Patients, Population, or Problem	A description of the patients of interest. It includes the condition(s), populations or sub-populations, disease severity or stage, co-occurring conditions, and other patient characteristics or demographics.
I	Intervention or Exposure	Refers to the specific treatments or approaches used with the patient or population. It includes doses, frequency, methods of administering treatments, etc.
C	Comparison	Describes the interventions or care that is being compared with the intervention(s) of interest described above. It includes alternatives such as placebo, drugs, surgery, lifestyle changes, standard of care, etc.
O	Outcome	Describes the specific results of interest. Outcomes can include short, intermediate, and long-term outcomes, or specific results such as quality of life, complications, mortality, morbidity, etc.
(T)	Timing, if applicable	Describes the duration of time that is of interest for the particular patient intervention and outcome, benefit, or harm to occur (or not occur).
(S)	Setting, if applicable	Describes the setting or context of interest. Setting can be a location (such as primary, specialty, or inpatient care).

The Champions, Work Group, and evidence review team carried out several iterations of this process, each time narrowing the scope of the CPG and the literature review by prioritizing the topics of interest. Due to resource constraints, all developed KQs were not able to be included in the systematic review. Thus, the Champions and Work Group determined which questions were of highest priority, and those were included in the review. Table E-4 contains the final set of KQs used to guide the systematic review for this CPG.

a. Population(s)

Adults 18 years or older with chronic cancer or non-cancer pain treated in any clinical setting were covered in this systematic review.

b. Intervention(s)

Table E-2 lists the interventions that were covered in this systematic review. The interventions are listed according to the KQs they address.

Table E-2. Key Question Specific Interventions

Question	Interventions
1	Patients with a co-occurring medical or psychological condition on the following opioids: ■ Buprenorphine ■ Codeine ■ Hydrocodone ■ Hydromorphone ■ Morphine ■ Oxycodone ■ Oxymorphone ■ Tapentadol ■ Tramadol ■ Fentanyl ■ Methadone
2	Opioid dosage Length of opioid use Other risk factors (others may be included)[255] ■ Age ■ Days with physical healthcare visits ■ Degree of pain ■ Gender ■ History of sexual abuse ■ History of abuse (including emotional, physical, or cyber bullying) or domestic violence ■ History of SUD—Self or familial ■ Marital status ■ Mental disorders ■ Non-opioid substance abuse ■ Race ■ Social status ■ Work status
3	See list of opioids under KQ1; non-pharmacological interventions
4	See list of opioids under KQ1; non-pharmacological interventions

Question	Interventions
5	Short-acting opioids ■ Codeine ■ Fentanyl ■ Hydrocodone (only in combination with acetaminophen and ibuprofen) ■ Hydromorphone ■ Morphine sulfate (tablet/liquid) ■ Oxycodone (alone or in combination with acetaminophen, ibuprofen, or aspirin) ■ Oxymorphone ■ Tramadol Long-acting/ER opioids ■ Buprenorphine transdermal system ■ Fentanyl transdermal system ■ Hydrocodone bitartrate ER capsules/tablets ■ Hydromorphone hydrochloride ER tablets ■ Methadone hydrochloride tablets ■ Morphine sulfate and naltrexone ER capsules ■ Morphine sulfate ER capsules/tablets ■ Oxycodone hydrochloride and naloxone hydrochloride ER tablets ■ Oxycodone hydrochloride ER tablets ■ Oxymorphone hydrochloride ER tablets ■ Tapentadol ER oral tablets ■ Transdermal, buccal, sublingual, or pumps See main list of opioids. ■ Abuse deterrent formulations ■ Buprenorphine/Naloxone ■ Morphine/Naltrexone ■ OROS hydromorphone (Osmotic ER Oral delivery System) ■ Oxycodone Controlled Release ■ Oxymorphone ■ Additional medications ■ Tramadol and other dual-mechanism opioids ■ Buprenorphine ■ Methadone
6	Opioid therapy plus other psychoactive medications such as CNS depressants/antidepressants, non-opioid analgesics, benzodiazepines, stimulants, muscle relaxers, medical marijuana, Z-drugs (e.g., Zolpidem [Ambien], Eszopiclone [Lunesta], Zaleplon [Sonata]), and over-the-counter sleep medications (e.g., diphenhydramine hydrochloride or doxylamine succinate)

Question	Interventions
7	Naloxone rescue with one form of naloxone Informed consent Use of written informed consent (previously called contracts) Risk assessment instruments Opioid management plans Patient education UDT PDMP Monitoring instruments More frequent monitoring Pill counts Use of abuse–deterrent formulations Diversion prevention interventions (e.g., properly securing drugs, medication take back programs, public health education) Pharmacogenetic testing Random call-backs Compliance with other therapies Case management Periodic check of state databases Needle exchange programs
8	Treatment with at least one of the following: ▪ Buprenorphine (with or without naloxone) ▪ Methadone ▪ Injectable/oral naltrexone ▪ Medical Management ▪ Contingency Management ▪ Individual Drug Counseling ▪ Motivational interviewing ▪ Motivational Enhancement Therapy ▪ Other motivational approaches
9	One tapering strategy or schedule

c. Comparator(s)

Table E-3 lists the comparators of interest to this systematic review. The comparators are listed by the KQ they address.

Table E-3. Key Question Specific Comparators

Question	Comparators
1	Patients without a co-occurring medical or mental health condition on LOT
2	Comparison groups that vary by LOT dosage and length of opioid use, other factors
3	No OT (including placebo) or other pain management strategies Other modalities: ■ Non-opioid medications (e.g., non-steroidal including compounded topical preparations) ■ Physical interventions (e.g., physical therapy, active/passive exercise, ultrasound stimulation, chiropractic, osteopathic manipulation therapy) ■ Behavioral/mental health interventions EXAMPLES: • CBT • Dialectical behavior therapy (DBT) • Mindfulness • Acceptance and commitment therapy (ACT) ■ Complementary and alternative interventions EXAMPLES: • Acupuncture • Chiropractic interventions
4	No OT (including placebo) or other pain management strategies Other modalities: ■ Non-opioid medications (e.g., non-steroidal including compounded topical preparations) ■ Physical interventions (e.g., physical therapy, active/passive exercise, ultrasound stimulation, chiropractic, osteopathic manipulation therapy) ■ Behavioral/ mental health interventions (e.g., CBT, ACT, mindfulness, DBT) ■ Complementary and alternative interventions
5	Long-acting opioid drugs or combination short and long-acting drugs (See list) Other route of administration/delivery alternatives Non abuse-deterrent formulations Other opioids No use of buprenorphine No use of methadone
6	Opioid therapy alone
7	No mitigation strategy or other mitigation strategy
8	No treatment for OUD or other treatment for OUD
9	Different tapering strategy or schedule

d. Outcomes

For the treatment and management questions (KQ 3–9), the following outcomes were of interest in the systematic review:

- Pain relief
- Quality of life
- Cognitive/functional status
- Mortality
- Opioid abuse/misuse

- Adverse events
  - SUD
  - Aberrant use
  - Overdose
  - Non-pain use of opiates
  - Abuse
  - Addictions
  - Cardiovascular events
  - Respiratory depression
  - Gastrointestinal complications (including constipation)
  - Endocrinological complications (including impotence)
  - Weight gain
  - Cognitive performance
  - Psychiatric decompensation
  - Psychological symptoms (e.g., depression, loss of libido, nightmares)
  - Headaches
  - Suicide
  - Accidents (including falls)
  - Infections
  - Increased risk of HIV and Hepatitis A, B, and C
  - Loss to follow-up/medical care

e. Timing

The timing considered in the systematic review was 12 weeks for studies looking at the efficacy of OT, and any follow-up for studies reporting on the safety of OT.

f. Setting

The setting considered in the systematic review was primary care.

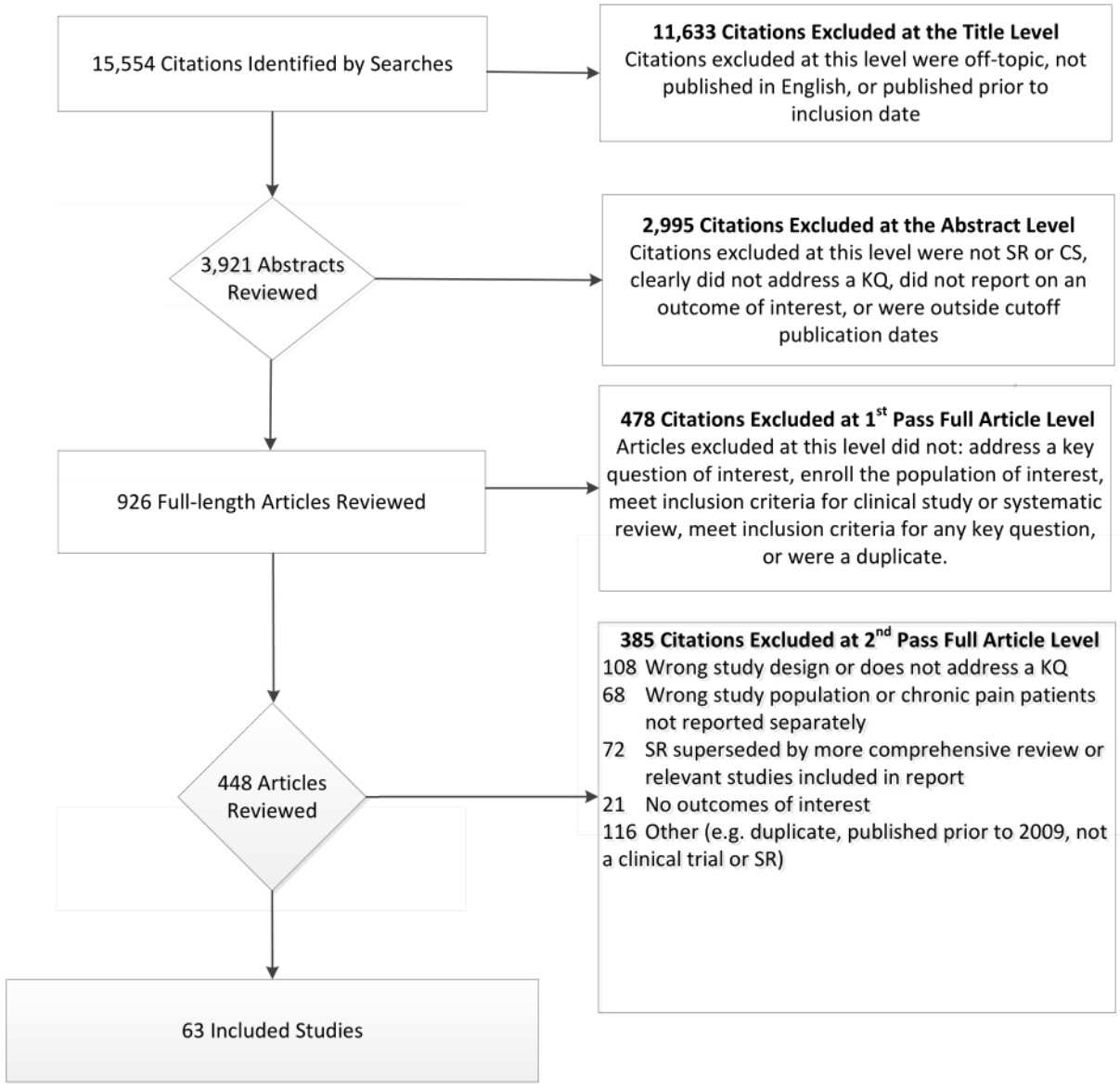
B. Conducting the Systematic Review

Extensive literature searches using the search terms and strategy included in Appendix J identified 15,554 citations potentially addressing the KQs of interest to this evidence review. Of those, 11,633 were excluded upon title review for clearly not meeting inclusion criteria (e.g., not pertinent to the topic, not published in English, published prior to study inclusion publication date, not a full-length article). Overall, 3,921 abstracts were reviewed with 2,995 of those being excluded for the following reasons: not a systematic review or clinical study (CS), did not address a KQ of interest to this review, did not enroll a population of

interest, or published prior to March 1, 2009. A total of 926 full-length articles were reviewed. Of those, 478 were excluded at a first pass review for the following: not addressing a KQ of interest, not enrolling the population of interest, not meeting inclusion criteria for CS or systematic review, not meeting inclusion criteria for any KQ, or being a duplicate. A total of 448 full-length articles were thought to address one or more KQs and were further reviewed. Of these, 385 were ultimately excluded. Reasons for their exclusion are presented in Figure E-1 below.

Overall, 63 articles addressed one or more of the KQs and were considered as evidence in this review. Table E-4 indicates the number of studies that addressed each of the questions.

Figure E-1. Study Flow Diagram


15,554 Citations Identified by Searches
11,633 Citations Excluded at the Title Level
Citations excluded at this level were off-topic, not published in English, or published prior to inclusion date
3,921 Abstracts Reviewed
2,995 Citations Excluded at the Abstract Level
Citations excluded at this level were not SR or CS, clearly did not address a KQ, did not report on an outcome of interest, or were outside cutoff publication dates
926 Full-length Articles Reviewed
478 Citations Excluded at 1st Pass Full Article Level
Articles excluded at this level did not: address a key question of interest, enroll the population of interest, meet inclusion criteria for clinical study or systematic review, meet inclusion criteria for any key question, or were a duplicate.
448 Articles Reviewed
385 Citations Excluded at 2nd Pass Full Article Level
108 Wrong study design or does not address a KQ
68 Wrong study population or chronic pain patients not reported separately
72 SR superseded by more comprehensive review or relevant studies included in report
21 No outcomes of interest
116 Other (e.g. duplicate, published prior to 2009, not a clinical trial or SR)
63 Included Studies

Abbreviations: CS: clinical study; KQ: key question; SR: systematic review

At the face-to-face meeting, sub-questions of KQs 3 and 4 were added assessing the safety and effectiveness of non-invasive treatments for chronic pain in patients not receiving OT. Searches to address these sub-questions were highly targeted to include systematic reviews only. Searches of EMBASE, PubMed, and PsycINFO were conducted through April 20, 2016. Five systematic reviews were included in the evidence base. Additionally, one systematic review was identified through hand searches of the literature and was also included in the final evidence base.

During the drafting process, two additional searches were performed. An additional search was added assessing the safety and effectiveness of take-home naloxone kits, a sub-question of KQ 7. Searches to address this intervention were highly targeted to include systematic reviews assessing use of take-home naloxone. Searches of EMBASE, PubMed, and PsycINFO were conducted through October 5, 2016. Two systematic reviews were included in the evidence base.

An additional sub-question assessing the need for follow-up after the prescription of opioids for acute pain was added to KQ 2 and an additional search was conducted. Searches to address this sub-question were broad, but the selection criteria were highly targeted to focus on prospective studies assessing risks associated with acute opioid use to treat acute pain. Searches of EMBASE, PubMed, and PsycINFO were conducted through December 20, 2016. Four retrospective cohorts and one secondary data analysis were included in the evidence base. Additionally, four studies already included in the evidence base for KQ 2 were used to inform the sub-question.

Table E-4. Evidence Base for Key Questions

Question Number	Question	Number and Type of Studies
1	What is the evidence that the following medical or mental health conditions are absolute or relative contraindications of prescribing long-term opioid therapy (LOT)? ■ Active pursuit of compensation ■ Centralized pain conditions such as fibromyalgia ■ Chronic obstructive pulmonary disease ■ Cognitive impairment ■ Depression ■ Headache ■ Gastrointestinal (GI) motility problems (e.g., toxic megacolon, GI pain syndromes, narcotic bowel syndrome) ■ Immune status changes ■ Inability to participate in comprehensive treatment plan ■ Incarceration (history of) ■ Hepatic, renal, or pulmonary disease ■ Suspected opioid misuse (e.g., overdose, early refills, diversion, taking more than prescribed) ■ Osteoporosis ■ Personality disorders ■ Posttraumatic stress disorder ■ Sleep disorders ■ Substance use disorders (SUD) (current or history of) ■ Suicidality ■ Traumatic brain injury ■ Use of medical marijuana ■ QT prolongation	12 cohort studies 1 case-cohort study 1 nested case-control study
2	What factors increase the risk of developing misuse or opioid use disorder (OUD) when considering LOT? a) What are the risks for long-term use associated with acute use of opioids in treating acute pain?	14 cohort studies 1 case-cohort study 1 nested case-control study 1 secondary data analysis
3	What is the comparative effectiveness of LOT versus other treatment modalities? a) What is the comparative effectiveness of LOT versus no opioid therapy or other treatment modalities for patients with a history of or current SUD? b) What is the effectiveness of non-pharmacological interventions in patients with chronic pain?	7 systematic reviews and 17 RCTs
4	What is the safety of LOT versus other treatment modalities? a) What is the safety of LOT versus other treatment modalities for patients with a history of or current SUD? b) What is the safety of non-pharmacological interventions in patients with chronic pain?	

Question Number	Question	Number and Type of Studies
5	What is the comparative effectiveness and safety of various opioid formulations? a) Immediate-release/short-acting opioids compared to ER/long-acting opioids b) Route of administration/ delivery alternatives such as transdermal, buccal, sublingual, pumps c) Abuse deterrent formulations compared to non-abuse deterrent formulations d) Tramadol and other dual-mechanism opioids e) Buprenorphine f) Methadone	2 systematic reviews and 7 RCTs
6	Does additional use of benzodiazepines or other psychoactive medications increase the risk of adverse events compared to opioid therapy alone?	1 RCT 1 prospective comparison trial 1 post-hoc pooled analysis 1 retrospective cohort study
7	What is the comparative effectiveness of different risk mitigation strategies for patients either on LOT or being considered for LOT? a) Does this differ for patients with history of or current SUD? b) Does this differ for patients with mental health comorbidities? c) Does this differ for patients with medical comorbidities? d) What is the safety and effectiveness of take-home naloxone kits?	3 systematic reviews 1 prospective cohort study 1 retrospective database study
8	What is the safety and effectiveness of treatment of OUD (diagnosed or suspected) in patients with chronic pain? a) Do outcomes vary by severity of OUD?	1 systematic review and 2 RCTs
9	What is the safety and effectiveness of different tapering strategies and schedules?	1 RCT 1 prospective cohort study
Total Evidence Base (Note, some papers were used for more than one KQ)		**63 Studies**

a. Criteria for Study Inclusion/Exclusion

i. General Criteria

- Clinical studies or systematic reviews published on or after March 1, 2009 to January 18, 2016. For sub-questions of KQs 3 and 4, systematic reviews published through April 20, 2016 were included. For a sub-question of KQ 7, systematic reviews published through October 5, 2016 were included. For a sub-question of KQ 2, clinical studies or systematic reviews published through December 20, 2016 were included. If multiple systematic reviews addressed a KQ, the most recent and/or comprehensive review was selected. Systematic reviews were supplemented with clinical studies published subsequent to the systematic review.
- Studies must have been published in English.
- Publication must have been a full CS or systematic review; abstracts alone were not included. Similarly, letters, editorials, and other publications that were not full-length clinical studies were not accepted as evidence.

- Study must have enrolled at least 20 patients (10 per study group) unless otherwise noted (see Key Question Specific Criteria below).
- Study must have reported on an outcome of interest. Study must have enrolled a patient population in which at least 80% of patients were receiving OT for chronic pain of at least 12 weeks' duration (except for the sub-question of KQ 2a pertaining to risks associated with acute opioid use in acute pain, and KQ 7d on naloxone rescue). If the percentage is less than 80%, then data must have been reported separately for this patient subgroup.
- For outcomes measuring treatment effectiveness, patients must have been followed for at least 12 weeks.
- For KQ specific criteria, in the event that one or more KQs did not have sufficient evidence from the study designs specified below, lower-level evidence was evaluated for that KQ(s). Lower-level evidence was considered on a question-by-question basis.

ii. Key Question Specific Criteria

- For KQ 1, acceptable study designs included systematic reviews, RCTs, or prospective cohort studies that statistically compared outcomes for patients with chronic pain and a co-occurring medical or mental health condition on OT to patients with chronic pain and no additional medical or mental health condition on OT. Large retrospective database studies (200 patients minimum) that performed multivariate statistical analyses of the effect of co-occurring conditions on patient outcomes were also acceptable.
- For KQ 2, acceptable study designs included systematic reviews, RCTs, or prospective cohort studies that statistically compared outcomes for patients with chronic pain and differences in potential risk factors for developing opioid misuse or OUD. For LTOT, large retrospective database studies (200 patients minimum) that performed multivariate statistical analyses of the effect of risk factors on patient outcomes were also acceptable. For KQ 2a, studies were limited to prospective study design.
- For KQs 3-6, 8, and 9, acceptable study designs included systematic reviews of RCTs and/or individual RCTs.
- For KQ 7, acceptable study designs included systematic reviews of RCTs, individual RCTs, or nonrandomized comparative studies.

b. Literature Search Strategy

Information regarding the bibliographic databases, date limits, and platform/provider can be found in Table E-5, below. Additional information on the search strategies, including topic-specific search terms and search strategies can be found in Appendix J.

Table E-5. Bibliographic Database Information

Name	Date Limits	Platform/Provider
Bibliographic Databases		
The Cochrane Central Register of Controlled Trials (CENTRAL)	11/24/15	Wiley
The Cochrane Database of Methodology Reviews (Methodology Reviews)	11/24/15	Wiley

Name	Date Limits	Platform/Provider
The Cochrane Database of Systematic Reviews (Cochrane Reviews)	11/24/15	Wiley
Database of Abstracts of Reviews of Effects	11/24/15	Wiley
EMBASE (Excerpta Medica)	12/20/16	Elsevier
Health Technology Assessment Database (HTA)	11/24/15	Wiley
MEDLINE/PreMEDLINE	12/20/16	OVIDSP
PsycINFO	12/21/16	OVIDSP
PubMed (In-process and Publisher records)	12/20/16	NLM
Gray Literature Resources		
AHRQ	11/30/15	AHRQ
Healthcare Standards database	11/30/15	ECRI Institute
National Guideline Clearinghouse™	11/30/15	AHRQ
National Institute of Health and Clinical Excellence	11/30/15	NHS

C. Convening the Face-to-face Meeting

In consultation with the COR, the Champions, and the Work Group, the Lewin Team convened a three and a half day face-to-face meeting of the CPG Champions and Work Group on April 5-8, 2016. These experts were gathered to develop and draft the clinical recommendations for an update to the 2010 OT CPG. Lewin presented findings from the evidence review of KQs 1-9 in order to facilitate and inform the process.

Under the direction of the Champions, the Work Group was charged with interpreting the results of the evidence review, and asked to categorize and carry forward recommendations from the 2010 OT CPG, modifying the recommendations as necessary. The members also developed new clinical practice recommendations not presented in the 2010 OT CPG, based on the 2016 evidence review. The subject matter experts were divided into two smaller subgroups at this meeting.

As the Work Group drafted clinical practice recommendations, they also assigned a grade for each recommendation based on a modified GRADE and USPSTF methodology. Each recommendation was graded by assessing the quality of the overall evidence base, the associated benefits and harms, the variation in values and preferences, and other implications of the recommendation.

In addition to developing recommendations during the face-to-face meeting, the Work Group also revised the 2010 OT CPG algorithm to reflect the new and amended recommendations. They discussed the available evidence as well as changes in clinical practice since 2010, as necessary, to update the algorithm.

D. Grading Recommendations

This CPG uses the GRADE methodology to assess the quality of the evidence base and assign a grade for the strength for each recommendation. The GRADE system uses the following four domains to assess the strength of each recommendation:[68]

- Balance of desirable and undesirable outcomes
- Confidence in the quality of the evidence
- Values and preferences

- Other implications, as appropriate, e.g.,:
  - Resource Use
  - Equity
  - Acceptability
  - Feasibility
  - Subgroup considerations

The following sections further describe each domain.

Balance of desirable and undesirable outcomes refers to the size of anticipated benefits (e.g., increased longevity, reduction in morbid event, resolution of symptoms, improved quality of life, decreased resource use) and harms (e.g., decreased longevity, immediate serious complications, adverse event, impaired quality of life, increased resource use, inconvenience/hassle) relative to each other. This domain is based on the understanding that the majority of clinicians will offer patients therapeutic or preventive measures as long as the advantages of the intervention exceed the risks and adverse effects. The certainty or uncertainty of the clinician about the risk-benefit balance will greatly influence the strength of the recommendation.

Some of the discussion questions that fall under this domain include:

- Given the best estimate of typical values and preferences, are you confident that the benefits outweigh the harms and burden or vice versa?
- Are the desirable anticipated effects large?
- Are the undesirable anticipated effects small?
- Are the desirable effects large relative to undesirable effects?

Confidence in the quality of the evidence reflects the quality of the evidence base and the certainty in that evidence. This second domain reflects the methodological quality of the studies for each outcome variable. In general, the strength of recommendation follows the level of evidence, but not always, as other domains may increase or decrease the strength. The evidence review used for the development of recommendations for LOT, conducted by ECRI, assessed the confidence in the quality of the evidence base and assigned a rate of “High,” “Moderate,” “Low,” or “Very Low.”

The elements that go into the confidence in the quality of the evidence include:

- Is there high or moderate quality evidence that answers this question?
- What is the overall certainty of this evidence?

Values and preferences is an overarching term that includes patients’ perspectives, beliefs, expectations, and goals for health and life. More precisely, it refers to the processes that individuals use in considering the potential benefits, harms, costs, limitations, and inconvenience of the therapeutic or preventive measures in relation to one another. For some, the term “values” has the closest connotation to these processes. For others, the connotation of “preferences” best captures the notion of choice. In general,

values and preferences increase the strength of the recommendation when there is high concordance and decrease it when there is great variability. In a situation in which the balance of benefits and risks are uncertain, eliciting the values, concerns, and preferences of patients and empowering them or their surrogates to make decisions consistent with patient goals of care becomes even more important. A recommendation can be described as having "similar values," "some variation," or "large variation" in typical values and preferences between patients and the larger populations of interest.

Some of the discussion questions that fall under the purview of values and preferences include:

- Are you confident about the typical values and preferences and are they similar across the target population?
- What are the patient's values and preferences?
- Are the assumed or identified relative values similar across the target population?

Other implications consider the practicality of the recommendation, including resources use, equity, acceptability, feasibility and subgroup considerations. Resource use is related to the uncertainty around the cost-effectiveness of a therapeutic or preventive measure. For example statin use in the frail elderly and others with multiple co-occurring conditions may not be effective and depending on the societal benchmark for willingness to pay, may not be a good use of resources. Equity, acceptability, feasibility, and subgroup considerations require similar judgments around the practically of the recommendation.

The framework below (Table E-6) was used by the Work Group to guide discussions on each domain.

Table E-6. Evidence to Recommendation Framework

Decision Domain	Judgment
Balance of desirable and undesirable outcomes	
▪ Given the best estimate of typical values and preferences, are you confident that the benefits outweigh the harms and burden or vice versa? ▪ Are the desirable anticipated effects large? ▪ Are the undesirable anticipated effects small? ▪ Are the desirable effects large relative to undesirable effects?	Benefits outweigh harms/burden Benefits slightly outweigh harms/burden Benefits and harms/burden are balanced Harms/burden slightly outweigh benefits Harms/burden outweigh benefits
Confidence in the quality of the evidence	
▪ Is there high- or moderate quality evidence that answers this question? ▪ What is the overall certainty of this evidence?	High Moderate Low Very low
Values and preferences	
▪ Are you confident about the typical values and preferences and are they similar across the target population? ▪ What are the patient's values and preferences? ▪ Are the assumed or identified relative values similar across the target population?	Similar values Some variation Large variation
Other implications (e.g., resource use, equity, acceptability, feasibility, subgroup considerations)	
▪ Are the resources worth the expected net benefit from the recommendation? ▪ What are the costs per resource unit? ▪ Is this intervention generally available? ▪ Is this intervention and its effects worth withdrawing or not allocating resources from other interventions? ▪ Is there lots of variability in resource requirements across settings?	Various considerations

The strength of a recommendation is defined as the extent to which one can be confident that the desirable effects of an intervention outweigh its undesirable effects and is based on the framework above, which combines the four domains.[68] GRADE methodology does not allow for recommendations to be made based on expert opinion alone. While strong recommendations are usually based on high or moderate confidence in the estimates of effect (quality of the evidence) there may be instances where strong recommendations are warranted even when the quality of evidence is low.[256] In these types of instances where the balance of desirable and undesirable outcomes and values and preferences played large roles in determining the strength of a recommendation, this is explained in the discussion section for the recommendation.

The GRADE of a recommendation is based on the following elements:

- Four decision domains used to determine the strength and direction (described above)
- Relative strength (Strong or Weak)
- Direction (For or Against)

The relative strength of the recommendation is based on a binary scale, "Strong" or "Weak." A strong recommendation indicates that the Work Group is highly confident that desirable outcomes outweigh undesirable outcomes. If the Work Group is less confident of the balance between desirable and undesirable outcomes, they present a weak recommendation.

Similarly, a recommendation for a therapy or preventive measure indicates that the desirable consequences outweigh the undesirable consequences. A recommendation against a therapy or preventive measure indicates that the undesirable consequences outweigh the desirable consequences.

Using these elements, the grade of each recommendation is presented as part of a continuum:

- Strong For (or "We recommend offering this option …")
- Weak For (or "We suggest offering this option …")
- Weak Against (or "We suggest not offering this option …")
- Strong Against (or "We recommend against offering this option …")

Note that weak (For or Against) recommendations may also be termed "Conditional," "Discretionary," or "Qualified." Recommendations may be conditional based upon patient values and preferences, the resources available, or the setting in which the intervention will be implemented. Recommendations may be at the discretion of the patient and clinician, or they may be qualified with an explanation about the issues that would lead decisions to vary.

E. Recommendation Categorization

a. Categorizing Recommendations with an Updated Review of the Evidence

Recommendations were first categorized by whether or not they were based on an updated review of the evidence. If evidence had been reviewed, recommendations were categorized as "New-added," "New-replaced," "Not changed," "Amended," or "Deleted."

"Reviewed, New-added" recommendations were original, new recommendations that were not in the 2010 OT CPG. "Reviewed, New-replaced" recommendations were in the previous version of the guideline, but were modified to align with the updated review of the evidence. These recommendations could have also included clinically significant changes to the previous version. Recommendations categorized as "Reviewed, Not changed" were carried forward from the previous version of the CPG unchanged.

To maintain consistency between 2010 recommendations, which were developed using the USPSTF methodology, and 2017 recommendations, which were developed using the GRADE methodology, it was necessary to modify the 2010 recommendations to include verbiage to signify the strength of the recommendation (e.g., "We recommend," "We suggest"). Because the 2010 recommendations inherently needed to be modified at least slightly to include this language, the "Not changed" category was not used. For recommendations carried forward to the updated CPG with review of the evidence and slightly modified wording, the "Reviewed, Amended" recommendation category was used. This allowed for the wording of the recommendation to reflect GRADE methodology as well as for any other non-substantive (i.e., not clinically meaningful) language changes deemed necessary. The evidence used to support these

recommendations was carried forward from the previous version of the CPG and/or was identified in the evidence review for the update.

Recommendations could have also been designated "Reviewed, Deleted." These were recommendations from the previous version of the CPG that were not brought forward to the updated guideline after review of the evidence. This occurred if the evidence supporting the recommendations was out of date, to the extent that there was no longer any basis to recommend a particular course of care and/or new evidence suggests a shift in care, rendering recommendations in the previous version of the guideline obsolete.

b. Categorizing Recommendations without an Updated Review of the Evidence

There were also cases in which it was necessary to carry forward recommendations from the previous version of the CPG without a systematic review of the evidence. Due to time and budget constraints, the update of the OT CPG could not review all available evidence on management of LOT, but instead focused its KQs on areas of new or updated scientific research or areas that were not previously covered in the CPG.

For areas of research that have not changed, and for which recommendations made in the previous version of the guideline were still relevant, recommendations could have been carried forward to the updated guideline without an updated systematic review of the evidence. The support for these recommendations in the updated CPG was thus also carried forward from the previous version of the CPG. These recommendations were categorized as "Not reviewed." If evidence had not been reviewed, recommendations could have been categorized as "Not changed," Amended," or "Deleted."

"Not reviewed, Not changed" recommendations refer to recommendations from the previous version of the OT CPG that were carried forward unchanged to the updated version. The category of "Not reviewed, Amended" was used to designate recommendations that were modified from the 2010 CPG with the updated GRADE language, as explained above.

Recommendations could also have been categorized as "Not reviewed, Deleted" if they were determined to be out of scope. A recommendation was out of scope if it pertained to a topic (e.g., population, care setting, treatment, condition) outside of the scope for the updated CPG as defined by the Work Group.

The categories for the recommendations included in the 2017 version of the guideline are noted in the Recommendations. The categories for the recommendations from the 2010 OT CPG are noted in Appendix H.

c. Recommendation Categories and Definitions

For use in the 2017 OT CPG, a set of recommendation categories was adapted from those used by the United Kingdom National Institute for Health and Clinical Excellence (NICE).[72,73] These categories, along with their corresponding definitions, were used to account for the various ways in which recommendations could have been updated from the 2010 OT CPG. The categories and definitions can be found in Table E-7.

Table E-7. Recommendation Categories and Definitions

Evidence Reviewed*	Recommendation Category*	Definition*
Reviewed	New-added	New recommendation following review of the evidence
	New-replaced	Recommendation from previous CPG that has been carried over to the updated CPG that has been changed following review of the evidence
	Not changed	Recommendation from previous CPG that has been carried forward to the updated CPG where the evidence has been reviewed but the recommendation is not changed
	Amended	Recommendation from the previous CPG that has been carried forward to the updated CPG where the evidence has been reviewed and a minor amendment has been made
	Deleted	Recommendation from the previous CPG that has been removed based on review of the evidence
Not reviewed	Not changed	Recommendation from previous CPG that has been carried forward to the updated CPG, but for which the evidence has not been reviewed
	Amended	Recommendation from the previous CPG that has been carried forward to the updated CPG where the evidence has not been reviewed and a minor amendment has been made
	Deleted	Recommendation from the previous CPG that has been removed because it was deemed out of scope for the updated CPG

*Adapted from the NICE guideline manual (2012) [72] and Garcia et al. (2014) [73]
Abbreviation: CPG: clinical practice guideline

F. Drafting and Submitting the Final Clinical Practice Guideline

Following the face-to-face meeting, the Champions and Work Group members were given writing assignments to craft discussion sections to support each of the new recommendations and/or to update discussion sections from the 2010 OT CPG to support the amended "carried forward" recommendations. The Work Group also considered tables, appendices, and other sections from the 2010 OT CPG for inclusion in the update. During this time, the Champions and Work Group also made additional revisions to the algorithm, as necessary.

After developing the initial draft of the updated CPG, an iterative review process was used to solicit feedback on and make revisions to the CPG. Once they were developed, the first two drafts of the CPG were posted on a wiki website for a period of 14-20 business days for internal review and comment by the Work Group. All feedback submitted during each review period was reviewed and discussed by the Work Group and appropriate revisions were made to the CPG.

Draft 3 of the CPG was made available for peer review and comment. This process is described in Peer Review Process. After revisions were made based on the feedback received during the peer review and comment period, the Champions presented the CPG to the EBPWG for their approval. Changes were made based on feedback from the EBPWG and the guideline was finalized.

The Work Group also produced a set of guideline toolkit materials, which included a provider summary, pocket card, and a patient summary. The final 2017 OT CPG was submitted to the EBPWG in February 2017.

Appendix F: Patient Focus Group Methods and Findings

A. Methods

On December 14, 2015, as part of the effort to update this CPG, the VA and DoD Leadership, along with the OT CPG Work Group, held a patient focus group at the Washington DC VA Medical Center. Focus group participants included six patients and two family caregivers. One additional family caregiver was interviewed separately at a later date.

The aim of the focus group and interview was to further the understanding of the perspectives of patients receiving LOT within the VA and/or DoD healthcare systems, as these patients are most affected by the recommendations put forth in the updated OT CPG. The focus group and interview explored patient perspectives on a set of topics related to management of OT in the VA and DoD healthcare systems, including knowledge of OT and other pain treatment options, delivery of care, and the impact of and challenges with LOT.

Participants for the focus group were recruited from the pain clinics at the Walter Reed National Military Medical Center and the Washington DC VA Medical Center. Patient focus group participants were not intended to be a representative sample of VA and DoD patients who have experienced LOT. However, recruitment focused on eliciting a range of perspectives likely to be relevant and informative in the guideline development process. Patients were not incentivized for their participation or reimbursed for travel expenses.

The OT CPG Champions and Work Group developed a set of questions to help guide the focus group and interview. The facilitator from Lewin led the discussion using interview questions prepared by the Work Group as a general guide to elicit the most important information from the patients regarding their experiences and views about their treatment and overall care. Given the limited time and the range of interests and expressiveness of the participants, not all of the listed questions were addressed.

At the time of the focus group, three patients were receiving care in the DoD healthcare system, two patients were receiving care in the VA healthcare system, and one patient was receiving care from a private pain center. Some of these patient participants had transitioned between multiple care settings, including from VA to DoD, from DoD to VA, and from a governmental healthcare setting to a private healthcare setting. Two patients stated that they were currently on LOT for pain. Four patients stated that they had previously been on LOT, but have since transitioned to other treatments for pain.

The following concepts are aspects of care that are important to patients and family caregivers that emerged from the focus group discussion and the interview. Each of these themes was an important and needed aspect of participants' healthcare.

B. Patient Focus Group Findings

Using shared decision making, consider all treatment options and develop treatment plan based on the balance of risks, benefits, and patient-specific goals, values, and preferences

- Identify patient-specific goals associated with LOT (main goals of these focus group participants included returning to work, minimizing pain, maintaining a functional life, avoiding invasive medical procedures, and getting off opioids)
- Discuss and consider all pain management options (non-pharmacotherapy and non-opioid pharmacotherapy) prior to starting LOT; do not default to prescribing opioids
- Use shared decision making to develop an individualized treatment plan; discuss pros and cons (e.g., benefits, risks, side effects) of each treatment option (including non-opioid treatment options) in conjunction with each patient's goals, priorities, values, and preferences
- Maintain focus on patient goals throughout treatment, including any changes in those goals over time

Modify treatment based on patient response, considering patient-specific goals, values, and preferences

- Be prepared to adjust or otherwise change treatment (e.g., tapering opioids) subject to patient response, preferences, and changes in priorities and goals; convey this flexibility and support the patient and support him/her during the change in treatment
- Do not continue to prescribe opioids when patients express reluctance to take them or do not adhere; continue to understand patient needs and preferences and adapt treatment accordingly
- Take time to develop a thorough understanding of patient needs and capabilities; develop an individualized treatment plan; be accountable for adverse outcomes
- Even after LOT is initiated, continue to discuss and consider all pain management options (non-pharmacotherapy and non-opioid pharmacotherapy)
- Carefully consider side effects during monitoring and adjust treatment in order to minimize side effects (e.g., depression, weight gain, headaches, nightmares, problems with intimacy, paresthesias) pursuant to individual patient preferences

Involve family caregivers in accordance with patient preferences and maintain open, trusting, and respectful relationship with patients and family caregivers

- Foster family, including family caregiver, involvement in shared decision making and support in accordance with patient preferences and in a way that is beneficial to the patient
- Always treat patients and family, including family caregivers, with respect and support
- Build and maintain trust, respect, and support in relationship with the patient and family, including family caregivers
- Ensure the patient has the capability to engage in shared decision making; recognize that patients who are in pain or who are taking opioids or other powerful medications may be in

suboptimal condition to make informed decisions on their own and may benefit from involvement of knowledgeable family members, including family caregivers

Educate patients regarding treatment plan, alternative treatment options, and monitoring

- Clinicians should be proactive and responsive in providing necessary clinical information in a manner comprehensible to patients and family caregivers; acknowledge that patients will seek and acquire information from other sources (especially the Internet) and encourage patient proactivity
- When prescribing opioids, provide in-depth and patient-specific education on medication (e.g., side effects, dosing, administration, storage, safety, disposal, take back programs) during medical visits in conjunction with distributing or otherwise enabling access to educational materials
- Provide necessary information regarding changes in treatment; discuss tapering and risks of self-tapering as necessary; recognize and address the challenges for patients on OT, including tapering
- Explain/provide education to patients as to why doctors use monitoring practices such as UDT when patients are using opioids; do not simply order the tests without such explanation

Within and between healthcare systems, work with appropriate providers to ensure continuity of high quality care

- Consult with other providers (e.g., psychologists, physical therapists) and patient advocates as appropriate, especially when patients express the need for more information or other clinical support
- Provide seamless transitions in opioid treatment and other pain management within and between VA, DoD, and any other healthcare systems; patients should not have to encounter abrupt changes in treatment regimens moving from one system to another or have to "start all over" when moving to another system
- Continue transformation of pain management

Organize treatment to encourage patient adherence and participation

- Facilitate appointment scheduling for days and times that fit the patient's needs (e.g., try to avoid patient work days where possible, schedule multiple provider appointments on same day rather than multiple days)
- Facilitate prescription refills and patient visits for refills in a way that fits the patient's needs, lifestyle, and schedule, while maintaining safe prescribing practices

Acknowledge and minimize effects of potential medical error and take action to prevent future medical error

- Acknowledge instances of potential medical error or other instances in which patient outcomes from previous medical procedures were less than desirable or expected (including experiences

of adverse events) and the consequences for the patient; consider these experiences when developing treatment plans

- Report potential medical errors that may have been experienced by patients and take action to prevent future medical error

Appendix G: Evidence Table

#	Recommendation	2010 Grade[15]	Evidence[16]	Strength of Recommendation[17]	Recommendation Category[18]
1.	a) We recommend against initiation of long-term opioid therapy for chronic pain. b) We recommend alternatives to opioid therapy such as self-management strategies and other non-pharmacological treatments. c) When pharmacologic therapies are used, we recommend non-opioids over opioids.	None None None	[80-83,85] **Additional References:** [3,26,84]	a) Strong against b) Strong for c) Strong for	Reviewed, New-replaced
2.	If prescribing opioid therapy for patients with chronic pain, we recommend a short duration. Note: Consideration of opioid therapy beyond 90 days requires re-evaluation and discussion with patient of risks and benefits.	None	[86-89] **Additional References:** [132]	Strong for	Reviewed, New-replaced

[15] The 2010 VA/DoD OT CPG used the USPSTF evidence grading system (http://www.uspreventiveservicestaskforce.org). Inclusion of more than one 2010 Grade indicates that more than one 2010 CPG recommendation is covered under the 2016 recommendation. The strength of recommendations were rated as follows: A- a strong recommendation that the clinicians provide the intervention to eligible patients; B- a recommendation that clinicians provide (the service) to eligible patients; C- no recommendation for or against the routine provision of the intervention is made; D- recommendation is made against routinely providing the intervention; I- the conclusion is that the evidence is insufficient to recommend for or against routinely providing the intervention. "None" indicates that the 2017 OT CPG recommendation replaced or amended a 2010 OT CPG recommendation for which there was no grade. "N/A" indicates that the 2017 OT CPG recommendation was a new recommendation, and therefore does not have an associated 2010 Grade.

[16] The evidence column indicates studies that support each recommendation. For new recommendations, developed by the 2016 guideline Work Group, the literature cited corresponds directly to the 2016 evidence review. For recommendations that have been carried over from the 2010 VA/DoD OT CPG, slight modifications were made to the language in order to better reflect the current evidence and/or the change in grading system used for assigning the strength of each recommendation (USPSTF to GRADE). For these "modified" recommendations, the evidence column indicates "additional evidence," which can refer to either 1) studies that support the recommendation and which were identified through the 2016 evidence review, or 2) relevant studies that support the recommendation, but which were not systematically identified through a literature review.

[17] Refer to the Grading Recommendations section for more information on how the strength of the recommendation was determined using GRADE methodology.

[18] Refer to the Recommendation Categorization section for more information on the description of the categorization process and the definition of each category.

#	Recommendation	2010 Grade[15]	Evidence[16]	Strength of Recommendation[17]	Recommendation Category[18]
3.	For patients currently on long-term opioid therapy, we recommend ongoing risk mitigation strategies (see Recommendations 7-9), assessment for opioid use disorder, and consideration for tapering when risks exceed benefits (see Recommendation 14).	None	[86-89] **Additional References:** [132]	Strong for	Reviewed, New-replaced
4.	a) We recommend against long-term opioid therapy for pain in patients with untreated substance use disorder. b) For patients currently on long-term opioid therapy with evidence of untreated substance use disorder, we recommend close monitoring, including engagement in substance use disorder treatment, and discontinuation of opioid therapy for pain with appropriate tapering (see Recommendation 14 and Recommendation 17).	None	[59,61,66,86,87]	a) Strong against b) Strong for	Reviewed, Amended
5.	We recommend against the concurrent use of benzodiazepines and opioids. Note: For patients currently on long-term opioid therapy and benzodiazepines, consider tapering one or both when risks exceed benefits and obtaining specialty consultation as appropriate (see Recommendation 14 and the VA/DoD Clinical Practice Guideline for the Management of Substance Use Disorders).	N/A	[66] **Additional References:** [90,91]	Strong against	Reviewed, New-added
6.	a) We recommend against long-term opioid therapy for patients less than 30 years of age secondary to higher risk of opioid use disorder and overdose. b) For patients less than 30 years of age currently on long-term opioid therapy, we recommend close monitoring and consideration for tapering when risks exceed benefits (see Recommendation 14 and Recommendation 17).	None	[58,59,62,86-88,92,94] **Additional References:** [93,95-98]	a) Strong against b) Strong for	Reviewed, New-replaced

#	Recommendation	2010 Grade[15]	Evidence[16]	Strength of Recommendation[17]	Recommendation Category[18]
7.	We recommend implementing risk mitigation strategies upon initiation of long-term opioid therapy, starting with an informed consent conversation covering the risks and benefits of opioid therapy as well as alternative therapies. The strategies and their frequency should be commensurate with risk factors and include: ■ Ongoing, random urine drug testing (including appropriate confirmatory testing) ■ Checking state prescription drug monitoring programs ■ Monitoring for overdose potential and suicidality ■ Providing overdose education ■ Prescribing of naloxone rescue and accompanying education	None None None None None None B B	[61,99,100,107-109,114] **Additional References:** [24,33,53,101-106,110-113,115-122]	Strong for	Reviewed, New-replaced
8.	We recommend assessing suicide risk when considering initiating or continuing long-term opioid therapy and intervening when necessary.	None None	[61,123-128] **Additional References:** [129-131]	Strong for	Reviewed, Amended
9.	We recommend evaluating benefits of continued opioid therapy and risk for opioid-related adverse events at least every three months.	None None None None B	**Additional References:** [132]	Strong for	Reviewed, New-replaced
10.	If prescribing opioids, we recommend prescribing the lowest dose of opioids as indicated by patient-specific risks and benefits. Note: There is no absolutely safe dose of opioids.	None	[58,59,66,87,133,136] **Additional References:** [134,135]	Strong for	Reviewed, New-replaced
11.	As opioid dosage and risk increase, we recommend more frequent monitoring for adverse events including opioid use disorder and overdose. Note: ■ Risks for opioid use disorder start at any dose and increase in a dose dependent manner. ■ Risks for overdose and death significantly increase at a range of 20-50 mg morphine equivalent daily dose.	None	[58,59,66,87,133,136] **Additional References:** [134,135]	Strong for	Reviewed, New-replaced

#	Recommendation	2010 Grade[15]	Evidence[16]	Strength of Recommendation[17]	Recommendation Category[18]
12.	We recommend against opioid doses over 90 mg morphine equivalent daily dose for treating chronic pain. Note: For patients who are currently prescribed doses over 90 mg morphine equivalent daily dose, evaluate for tapering to reduced dose or to discontinuation (see Recommendations 14 and 15).	None	[58,59,66,87,133,136] **Additional References:** [134,135]	Strong against	Reviewed, New-replaced
13.	We recommend against prescribing long-acting opioids for acute pain, as an as-needed medication, or on initiation of long-term opioid therapy.	None	[140,141,143,144,146,149-159,163,165] **Additional References:** [10,137-139,142,145,147,148,160,162,164,166-169]	Strong against	Reviewed, New-replaced
14.	We recommend tapering to reduced dose or to discontinuation of long-term opioid therapy when risks of long-term opioid therapy outweigh benefits. Note: Abrupt discontinuation should be avoided unless required for immediate safety concerns.	N/A	**Additional References:** [10,137,170-175]	Strong for	Reviewed, New-added
15.	We recommend individualizing opioid tapering based on risk assessment and patient needs and characteristics. Note: There is insufficient evidence to recommend for or against specific tapering strategies and schedules.	N/A	**Additional References:** [10,137,170-175]	Strong for	Reviewed, New-added
16.	We recommend interdisciplinary care that addresses pain, substance use disorders, and/or mental health problems for patients presenting with high risk and/or aberrant behavior.	None None None None None	[114,176]	Strong for	Reviewed, New-replaced
17.	We recommend offering medication assisted treatment for opioid use disorder to patients with chronic pain and opioid use disorder. Note: See the VA/DoD Clinical Practice Guideline for the Management of Substance Use Disorders.	None None None	**Additional References:** [177-182]	Strong for	Reviewed, New-replaced

#	Recommendation	2010 Grade[15]	Evidence[16]	Strength of Recommendation[17]	Recommendation Category[18]
18.	a) We recommend alternatives to opioids for mild-to-moderate acute pain. b) We suggest use of multimodal pain care including non-opioid medications as indicated when opioids are used for acute pain. c) If take-home opioids are prescribed, we recommend that immediate-release opioids are used at the lowest effective dose with opioid therapy reassessment no later than 3-5 days to determine if adjustments or continuing opioid therapy is indicated. Note: Patient education about opioid risks and alternatives to opioid therapy should be offered.	N/A	[58,59,183-188]	a) Strong for b) Weak for c) Strong for	Reviewed, New-added

Appendix H: 2010 Recommendation Categorization Table

2010 Recommendation Location[19]			2010 Recommendation Text[20]	2010 Grade[21]	Category[22]	2016 Recommendation (if applicable)[23]
Module	Section	Number				
1	A	1	A trial of opioid therapy is indicated for a patient with chronic pain who meets all of the following criteria: a. Moderate to severe pain that has failed to adequately respond to indicated non-opioid and non- drug therapeutic interventions b. The potential benefits of opioid therapy are likely to outweigh the risks (i.e., no absolute contraindications) c. The patient is fully informed and consents to the therapy d. Clear and measurable treatment goals are established	None	Not reviewed, Deleted	
1	A	2	The ethical imperative is to provide the pain treatment with the best benefit-to-harm profile for the individual patient.	None	Not reviewed, Deleted	

[19] The first three columns indicate the location of each recommendation within the 2010 OT CPG.

[20] The 2010 Recommendation Text column contains the wording of each recommendation from the 2010 OT CPG.

[21] The 2010 VA/DoD OT CPG used the U.S. Preventive Services Task Force (USPSTF) evidence grading system. http://www.uspreventiveservicestaskforce.org The strength of recommendations were rated as follows: A- a strong recommendation that the clinicians provide the intervention to eligible patients; B- a recommendation that clinicians provide (the service) to eligible patients; C- no recommendation for or against the routine provision of the intervention is made; D- recommendation is made against routinely providing the intervention; I- the conclusion is that the evidence is insufficient to recommend for or against routinely providing the intervention. "None" indicates there was no grade assigned to the recommendation in the 2010 OT CPG.

[22] The Category column indicates the way in which each 2010 OT CPG recommendation was updated.

[23] For recommendations that were carried forward to the 2010 OT CPG, this column indicates the new recommendation(s) to which they correspond.

2010 Recommendation Location[19]			2010 Recommendation Text[20]	2010 Grade1[21]	Category[22]	2016 Recommendation (if applicable)[23]
Module	Section	Number				
1	B	1	A comprehensive patient assessment should be completed to identify clinical conditions that may interfere with the appropriate and safe use of opioid therapy (OT). The comprehensive assessment should include: a. Medical History • Age, Sex • History of present illness, including a complete pain assessment (see Annotation C) • History of injury if applicable • Past Medical and Surgical history • Past Psychiatric history (including depression, anxiety, other emotional disorders, risk of suicide including family history and previous suicidal attempts) • Medications (including current and past analgesics, their effectiveness, side effects, and tolerability, as well as drugs that may interact with opioid therapy) • Substance use history (personal, family, peer group) • Family history • Social history (including employment, cultural background, social network, marital history, and legal history, other behavioral patterns (i.e. impulse behaviors)) • Review of systems • Allergies • Abuse (sexual, physical and mental) b. Physical examination • A general examination • A pain-focused musculoskeletal and neurologic examination • Mental Status Examination (MSE) (Including level of alertness, ability to understand and follow instruction, and suicidal ideation) c. Review of diagnostic studies and assessments d. Evaluation of occupational risks and ability to perform duty	None	Not reviewed, Deleted	
1	B	2	Information from the pain history and physical exam should be reviewed to ensure that the patient has had an adequate therapeutic trial of non-opioid medication therapies.	None	Not reviewed, Deleted	
1	B	3	A urine drug test (UDT) (also referred to as urine drug screen (UDS)) should be used to screen for the presence of illegal drugs, unreported prescribed medication, or unreported alcohol use prior to starting therapy. [B]	B	Reviewed, Deleted	
1	B	4	Patients on chronic opioid therapy should be assessed for suicide risk at onset of therapy and regularly thereafter. High suicide risk is a relative contraindication for OT.	None	Reviewed, Amended	Recommendation 8

2010 Recommendation Location[19]			2010 Recommendation Text[20]	2010 Grade[21]	Category[22]	2016 Recommendation (if applicable)[23]
Module	Section	Number				
1	B	5	Opioid therapy should be used only after careful consideration of the risks and benefits.	None	Reviewed, New-replaced	Recommendation 1 Recommendation 2 Recommendation 3
1	C	1	Pain intensity should be evaluated at each visit.	None	Not reviewed, Deleted	
1	C	2	Intensity of pain should be measured using a numeric rating scale (0-10 scale) for each of the following: • current pain, • least pain in last week • "usual" or "average" pain in last week	None	Not reviewed, Deleted	
1	C	3	The patient's response to current pain treatments should be assessed using questions such as: • "What is your intensity of pain after taking (use of) your current treatment/medication?" • "How long does your pain relief last after taking your treatment/medication?" • "How does taking your treatment/medication affect your functioning?" (Note: some interventions may temporarily increase pain, so it may not be appropriate to ask these questions.)	None	Not reviewed, Deleted	
1	C	4	Other attributes of pain should be assessed as part of the comprehensive pain assessment: • Onset and duration, location, radiation, description (quality), aggravating and alleviating factors, behavioral manifestations of pain, and impact of pain • Temporal patterns and variations (e.g., diurnal, monthly, seasonal) • Current and past treatments for pain • Patient's expectations for pain relief	None	Not reviewed, Deleted	
1	C	5	If possible, determine the type of pain: • Differentiate between nociceptive and neuropathic pain • Consider further evaluation if needed (such as imaging, Electro Diagnostic Studies (EDS) or consultation) • Ask specifically whether the patient suffers from headache	None	Not reviewed, Deleted	

2010 Recommendation Location[19]			2010 Recommendation Text[20]	2010 Grade[21]	Category[22]	2016 Recommendation (if applicable)[23]
Module	Section	Number				
1	C	6	Assessment of function, to obtain a baseline, should include: (Consistent evaluation tool is helpful in providing evaluation of response to opioid therapy over time): • Cognitive function (attention, memory, and concentration) • Employment • Enjoyment of life • Emotional distress (depression and anxiety) • Housework, chores, hobbies, and other day to day activities • Sleep • Mobility • Self-care behaviors • Sexual function	None	Not reviewed, Deleted	
1	C	7	Information from the pain history and physical exam should be reviewed to ensure that the patient has had an adequate trial of non-opioid therapy.	None	Not reviewed, Deleted	
2	D	1	Opioid therapy trial should NOT be initiated in the following situations (absolute contraindications): a. Severe respiratory instability b. Acute psychiatric instability or uncontrolled suicide risk c. Diagnosed non-nicotine Substance Use Disorder (DSM-IV criteria) not in remission and not in treatment d. True allergy to opioid agents (cannot be resolved by switching agents) e. Co-administration of drug capable of inducing life-limiting drug-drug interaction f. QTc interval > 500 millisecond for using methadone g. Active diversion of controlled substances (providing the medication to someone for whom it was not intended) h. Prior adequate trials of specific opioids that were discontinued due to intolerance, serious adverse effects that cannot be treated, or lack of efficacy	None	Reviewed, Amended	Recommendation 4

2010 Recommendation Location[19]			2010 Recommendation Text[20]	2010 Grade[21]	Category[22]	2016 Recommendation (if applicable)[23]
Module	Section	Number				
2	D	2	Opioid therapy trial can be initiated with caution in the following situations. Consider consultation with appropriate specialty care to evaluate if potential benefits outweigh the risks of therapy. a. Patient receiving treatment for diagnosed Substance Use Disorder (DSM-IV criteria). (See Annotation P1) b. Medical condition in which OT may cause harm: • Patient with obstructive sleep apnea not on CPAP • Patients with central sleep apnea (See Annotation P2) • Chronic pulmonary disease (mild-moderate asthma, COPD) • Cardiac condition (QTc interval 450-500 milliseconds) that may increase risk of using methadone • Known or suspected paralytic ileus • Respiratory depression in unmonitored setting c. Risk for suicide or unstable psychiatric disorder d. Complicated pain • Headache not responsive to other pain treatment modalities e. Conditions that may impact adherence to OT: • Inability to manage opioid therapy responsibly (e.g., cognitively impaired) • Unwillingness or inability to comply with treatment plan • Unwillingness to adjust at-risk activities resulting in serious re-injury • Social instability • Mental Health disorders	None	Reviewed, Deleted	
2	D	3	Consider consultation with an appropriate specialist if legal or clinical problems indicate need for more intensive care related to opioid management. (See Annotation E – Indications for consultation).	None	Not reviewed, Deleted	
2	E	1	Refer to an Advanced Pain provider, or interdisciplinary pain clinic or program for evaluation and treatment a patient with persistent pain and any of the following conditions: a. Complex pain conditions or polytrauma b. Significant medical comorbidities that may negatively impact opioid therapy c. Situation requires management beyond the comfort level of the primary provider	None	Not reviewed, Deleted	
2	E	2	Refer to SUD Specialty Provider for evaluation and treatment patient whose behavior suggests addiction to substances (excluding nicotine).	None	Not reviewed, Deleted	

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Module	Section	Number				
2	E	3	Consider consultation with a SUD specialist to evaluate the risk of recurrent substance abuse or to assist with ongoing management.	None	Reviewed, New-replaced	Recommendation 16
2	E	4	Refer to Behavioral Health Specialty for evaluation and treatment a patient with any of the following conditions: a. Psychosocial problems or comorbidities that may benefit from behavioral disease/case management b. Uncontrolled, severe psychiatric disorders or those who are emotionally unstable c. Patients expressing thoughts or demonstrating behaviors suggestive of suicide risk	None	Not reviewed, Deleted	
2	E	5	Refer patients with significant headache to a neurologist for evaluation and treatment.	None	Not reviewed, Deleted	
2	E	6	Consider consultation with occupational health specialty if patient's occupation requires a high level of cognitive function.	None	Not reviewed, Deleted	
2	F	1	The clinician should assess the ability of the patient being considered for opioid therapy to be able to adhere to treatment requirements, as these patients are likely to do well and benefit from OT.	None	Not reviewed, Deleted	
2	F	2	The appropriateness of opioid therapy as a treatment modality for chronic pain and the level of risk for adverse outcomes should be determined based on the initial and ongoing assessment of the patient.	None	Not reviewed, Deleted	
2	F	3	For patients with history of drug abuse, psychiatric issues, or serious aberrant drug-related behaviors, initiation of a trial of OT in the primary care setting should only be considered if more frequent and stringent monitoring can be provided. In such situations, clinicians should strongly consider consultation with a mental health or addiction specialist.	None	Not reviewed, Deleted	
2	F	4	Young patients (less than 25 years old) are at higher risk for diversion and abuse and may benefit from more stringent monitoring.	None	Reviewed, New-replaced	Recommendation 6
2	F	5	The clinician should consider referring patients who have unstable co-occurring disorders (substance use, mental health illnesses, or aberrant drug related behaviors) and who are at higher risk for unsuccessful outcomes (see Annotation E).	None	Not reviewed, Deleted	
2	G	1	Involve the patient and family/caregiver in the educational process, providing written educational material in addition to discussion with patient/family.	None	Not reviewed, Deleted	

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Module	Section	Number				
2	G	2	Discuss the opioid pain care agreement (OPCA) in detail, and reinforce in subsequent visits (See Annotation H).	None	Reviewed, New-replaced	Recommendation 7
2	G	3	Provide, and document in the medical record, patient education on the following topics: • General Information: goals and expectations, addiction, tolerance, physical dependency, withdrawal symptoms • Patient responsibilities: prescriptions, adherence to treatment plan, obtaining medications from a single prescriber (or clinic) and single pharmacy, pain diary, feedback to the provider • Legal Issues • Instruction on how to take medication: importance of consistent dosing and timing, interaction with other drugs • Prophylactic treatment of adverse effects and management of constipation • Discussion of an individualized comprehensive care plan that may include, in addition to OT, physical therapy, occupational therapy, cognitive-behavioral therapy, acupuncture, manipulation, complementary and alternative medicine, other non-pharmacologic therapies, and other non-opioid agents.	None	Reviewed, New-replaced	Recommendation 7
2	H	1	Discuss a trial of opioid therapy with the patient, and obtain the patient's informed consent in a shared decision-making discussion. Document the informed consent discussion.	None	Not reviewed, Deleted	
2	H	2	Review and discuss a written Opioid Pain Care Agreement (OPCA) with the patient who is expected to receive daily opioid therapy for the treatment of chronic pain. The signed agreement can serve as documentation of an informed consent discussion. (For a sample agreement, see Appendix C)	None	Reviewed, New-replaced	Recommendation 7

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Module	Section	Number				
2	H	3	The responsibilities during therapy, of the provider and the patient, should be discussed with the patient and family. A discussion of patient responsibilities should be patient-centered and address the following issues : • Goals of therapy -- Partial pain relief and improvement in physical, emotional, and/or social functioning • The requirement for a single prescribing provider or treatment team • The limitation on dose and number of prescribed medications • Proscription against the patient changing dosage without discussing with provider • Monitoring patient adherence - discuss the role of random urine drug testing, the use of "pill counts" • A prohibition on use with alcohol, other sedating medications, or illegal drugs without discussing with provider • Agreement not to drive or operate heavy machinery until abatement of medication-related drowsiness • Responsibility to keep medication safe and secure • Prohibition of selling, lending, sharing or giving any medication to others • Limitations on refills: only by appointment, in person, and no extra refills for running out early (exceptions should be considered on an individual basis) • Compliance with all components of overall treatment plan (including consultations and referrals) • Adverse effects and safety issues such as the risk of dependence and addictive behaviors • The option of sharing information with family members and other providers, as necessary, with the patient's consent • Need for periodic re-evaluation of treatment • Reasons for stopping opioid therapy • Consequences of non-adherence with the treatment agreement.	None	Reviewed, Deleted	
2	H	4	Patient's refusal to sign an agreement as part of the initial and ongoing assessments of the patient's ability to adhere to the treatment plan and the level of risk for adverse outcomes (see Table 2, Annotation F). The prescription of therapy, in such cases, should be based on the individual patient and the benefits versus harm involved with therapy. The rationale for prescribing opioids without a signed agreement should be documented.	None	Not reviewed, Deleted	

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Module	Section	Number				
2	I	1	The treatment plan should be individually tailored to the patient's circumstances and to the characteristics of the patient's pain.	None	Not reviewed, Deleted	
2	I	2	Consider the use of other treatment approaches (such as supervised therapeutic exercise, biofeedback, or cognitive behavior approaches), which should be coordinated with the opioid therapy.	None	Reviewed, New-replaced	Recommendation 1
2	I	3	Consider establishing a referral and interdisciplinary team approach, if indicated.	None	Not reviewed, Deleted	
2	I	4	Establish a follow-up schedule to monitor treatment and patient progress.	None	Not reviewed, Deleted	
2	I	5	The treatment plan and patient preferences should be documented in the medical record.	None	Not reviewed, Deleted	
3	K1	1	Chronic pain is often a complex biopsychosocial condition. Clinicians who prescribe OT should routinely integrate psychotherapeutic interventions, functional optimization, interdisciplinary therapy, and other adjunctive non-opioid pain therapies.	None	Not reviewed, Deleted	
3	K1	2	Provide written and verbal education to the patient about the specific medication, anticipated adverse effects, dosing and administration, possible excessive sedation and symptoms of opioid withdrawal.	None	Not reviewed, Deleted	
3	K1	3	With patient consent, obtain a urine drug test (UDT) prior to initiating an OT trial and randomly at follow-up visits to confirm the appropriate use of opioids. A patient can refuse urine drug testing. The provider should take into consideration a patient's refusal to undergo urine drug testing as part of the ongoing assessment of the patient's ability to adhere to the treatment plan and the level of risk for adverse outcomes (see Annotation F, Table 2).	None	Reviewed, Deleted	

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Module	Section	Number				
3	K1	4	There is no evidence to recommend for or against the selection of any specific opioid: a. Using a shared decision-making process, select a specific opioid formulation, based on experience and knowledge that matches the individual's needs and specific medical conditions b. Consider patient preference, and agent that allows administration by the least invasive route c. Consider the ease of drug administration, patient's prior experience with, and level of tolerance to opioid medications, potential risk for misuse, abuse patterns, and local formulary guidance d. Transdermal fentanyl should be avoided in opioid naïve patients.	None	Reviewed, New-replaced	Recommendation 13
3	K1	5	Start the opioid therapy trial with a low dose and with one medication at a time.	None	Not reviewed, Deleted	
3	K1	6	Initiate a bowel regimen to prevent and treat constipation, which is anticipated with all opioids.	None	Not reviewed, Deleted	
3	K1	7	For continuous chronic pain, an agent with a long duration of action, such as controlled-release morphine or methadone is recommended.	None	Not reviewed, Deleted	
3	K1	8	Alternatively, short-acting opioids can be started, and later converted to long acting opioids. (See Annotation K2 - Titration)	None	Not reviewed, Deleted	
3	K1	9	Treatment of continuous chronic pain should be initiated with opioids on a defined and scheduled basis.	None	Not reviewed, Deleted	
3	K1	10	For episodic chronic pain, consider short-acting opioids (such as morphine, oxycodone, or hydrocodone), trying one medication at a time on a PRN (as needed) basis. Long-acting opioids should not be used on a PRN basis.	None	Not reviewed, Deleted	

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Module	Section	Number				
3	K1	11	When using methadone: a. Inform patients of the arrhythmia risk b. Ask patients about heart disease, arrhythmia, and syncope c. Obtain an electrocardiogram (ECG) to measure the QTc interval before starting methadone and once the dose is stabilized (maintenance phase). Measure the QTc annually thereafter if the patient history is positive for risk factors for prolonged QTc interval, or has known prolonged QTc interval. Perform additional electrocardiography if the methadone dosage exceeds 100 mg/day, or if the patient has unexplained syncope or seizures d. If the QTc interval is greater than 450ms, but less than 500ms, reevaluate and discuss with the patient the potential risks and benefits of therapy, and the need for monitoring the QTc more frequently e. If the QTc interval exceeds 500 ms, discontinue or taper the methadone dose and consider using an alternative therapy. Other contributing factors, such as drugs that cause hypokalemia, or QT prolongation should be eliminated whenever possible f. Be aware of interactions between methadone and other drugs that may prolong QTc interval, or slow the elimination of methadone, and educate patients about drug interaction.	None	Not reviewed, Deleted	
3	K2	1	Maintain close communication with patients and families, explicitly discussing the criteria for evaluating the effects of analgesic medications; doing so can help in defusing the anxiety that often accompanies visits to the physician.	None	Not reviewed, Deleted	
3	K2	2	Ask the patient to keep records of the time and dose of medication, the degree of pain relief, and the occurrence of adverse effects.	None	Not reviewed, Deleted	
3	K2	3	Documentation is essential, and should demonstrate the evaluation process—including consultation, prescriptions, and periodic review of patient status. Any change and consequent patient response should be documented in the record.	None	Not reviewed, Deleted	
3	K2	4	Follow up with the patient in no longer than 2 to 4 weeks after dosage modifications, or other treatment adjustments, basing the frequency of follow-up on the clinical situation (also see Annotation K3 – Maintenance Phase).	None	Reviewed, Deleted	
3	K2	5	Assess the patient for changes in biopsychosocial and spiritual domains but especially the diagnosis, trajectory of disease, and effect of adjuvant therapies.	None	Not reviewed, Deleted	

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Module	Section	Number				
3	K2	6	As with initial opioid selection and dosing, titration should be individualized according to the patient's age, health status, previous exposure to opioids, level of pain, comorbidities, potential drug interactions, the particular opioid formulation, the level (setting) of care, attainment of therapeutic goals, and predicted or observed harms.	None	Not reviewed, Deleted	
3	K2	7	If necessary, the daily dose may be increased by 25%-100% at a time. In general, smaller increments are appropriate for elderly or frail patients, those with likely low opioid tolerance, and patients experiencing unsatisfactory pain relief in the presence of some adverse effects. Larger increments may be used in patients with severe uncontrolled pain or likely high level of opioid tolerance. If the new dose is well tolerated but ineffective, additional increases in dose can be considered.	None	Not reviewed, Deleted	
3	K2	8	To ensure that the full effect from a dosage change has been manifested, and to avoid potential toxicity due to rapid accumulation of a drug, do not increase the dose more frequently than every five half-lives. In the case of methadone, upward dosage titration should not occur more frequently than every 7 days and perhaps longer (e.g., every 1 to 2 months), and only if there is no problem with daytime sedation, taking into consideration that there is wide interpatient variability in half-lives and responsiveness. (See Appendices E1 and F)	None	Not reviewed, Deleted	
3	K2	9	If possible, titrate only one drug at a time while observing the patient for additive effects. Maintain patients on as few medications as possible to minimize drug interactions and adverse events. Discontinue medications, especially adjuvant medications, which do not add substantially to patient function or comfort. Continue close assessment of patients prescribed multiple centrally acting/psychoactive medications.	None	Not reviewed, Deleted	
3	K2	10	If a medication provides less than satisfactory pain reduction despite increasing the dose as tolerated to a reasonable level (less than 200 mg/day morphine equivalent), evaluate for potential causes such as nonadherence and drug interactions (see Appendix E, Table E6– Drug Interactions), and consider changing to an alternate opioid medication.	None	Not reviewed, Deleted	
3	K2	11	Medication may be increased until limited by adverse effects or clear evidence of lack of efficacy. If a high dose of medication (greater than 200 mg/day morphine equivalent) provides no further improvement in function, consider consultation rather than further increasing the dose.	None	Not reviewed, Deleted	
3	K2	12	During the titration phase, reasonable supplemental (rescue) doses of a short acting opioid may be considered. (See Annotation K-4-Supplemental Dosing)	None	Not reviewed, Deleted	

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Module	Section	Number				
3	K2	13	Consider one or more of the following adjustments in therapy when there is an apparent loss of analgesic effect a. Further optimize adjuvant therapies b. Re-titrate the dose • Increase dose by 25-100%. • Do not increase the dose more frequently than every 5 half lives (for methadone or fentanyl no more than once a week), to ensure that the full effect from a dosage change has been manifested and to avoid potential toxicity due to rapid accumulation of a drug • If possible, titrate only one drug at a time, while observing the patient for additive effects. Inappropriate or ineffective medications should be tapered while titrating an appropriate pharmacologic regimen • Medication may be increased until treatment goals are met, intolerable adverse effects occur, or there is clear evidence of lack of efficacy c. Rotate to another opioid • Rotation between opioids may help to improve efficacy, reduce side effects and reduce dose escalation in some patients who are receiving long-term opioid therapy • Rotate to another agent based on equianalgesic table and titrate (see Appendix E, Table E6 for conversion factors) d. Refer or consult with advanced pain care (pain or palliative care specialist/pharmacist) • If the dose of opioid is large (more than 200mg/day morphine equivalent) • If opioid induced hyperalgesia or opioid tolerance is suspected e. Discontinue Opioid Therapy (See Annotation X).	None	Not reviewed, Deleted	
3	K2	14	For a patient with continuous pain, an agent with a long duration of action, such as controlled-release morphine or methadone, is recommended.	None	Not reviewed, Deleted	
3	K2	15	If short-acting opioids are effective and well tolerated, it may be possible to achieve equivalent pain relief with fewer daily doses of the medication by substituting an equivalent dose of long-acting opioid medication (such as methadone, morphine CR, oxycodone CR, or transdermal fentanyl). These long- acting medications may provide steadier serum levels and smoother pain control. They can be supplemented with doses of short-acting medication to control pain exacerbation.	None	Not reviewed, Deleted	

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Module	Section	Number				
3	K2	16	The conversion to a long-acting opioid should be based on an equianalgesic conversion (see Appendix E, Table E3 for conversion factors) and consideration of the incomplete cross-tolerance between opioids. To allow for incomplete cross-tolerance, in most cases, the starting conversion dose should be 50% to 67% of the calculated equianalgesic dose. A notable exception to this general rule is methadone, which has relatively little cross-tolerance with other opioids and should be started at a conversion dose that is based on the previous morphine- equivalent dose. Inexperienced clinicians should consult with an expert before initiating methadone; even in an opioid tolerant patient (see Appendix E, Table E-3, and Appendix F Methadone Dosing Recommendations).	None	Not reviewed, Deleted	
3	K2	17	Base the method of rotating opioids on the clinical situation. Either of the following two methods may be used: a. Step-wise Rotation: Reduce the old opioid dose by 25% to 50% decrements and replace the amount removed with an equianalgesic conversion dose of the new opioid. This method may be preferable when switching large doses of opioids. A disadvantage of this method is that the causative opioid(s) of new or worsening adverse effects during rotation would be difficult to identify. b. Single-step Rotation: Stop the old opioid and start the new opioid in an equianalgesic conversion dose. This method may be preferable when the old agent must be stopped immediately because of a hypersensitivity reaction. A disadvantage of this method is that pain may worsen if the new agent has a delayed peak analgesic effect (e.g., methadone) while the old agent has a relatively short offset of effects.	None	Not reviewed, Deleted	
3	K3	1	Maintain the lowest effective and well-tolerated dose. The optimal opioid dose is the one that achieves the goals of pain reduction and/or improvement in functional status and patient satisfaction with tolerable adverse effects.	None	Reviewed, New-replaced	Recommendation 10 Recommendation 11 Recommendation 12
3	K3	2	Recognize that the dose may need to be titrated up or down on basis of the patient's current biopsychosocial situation. (See Annotation K2 – Titration Phase)	None	Not reviewed, Deleted	

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Module	Section	Number				
3	K3	3	Assess patients at least every 1 to 6 months based on the following: a. Individualize and adjust visit frequencies based on patient characteristics, comorbidities, level of risk for potential drug misuse (i.e., diversion, addiction, abuse, and aberrant drug-related behavior), type of pain, and type and dose of opioids. No specific visit frequency applies to all patients b. Select a frequency that allows close follow-up of the patient's adverse effects, pain status, and appropriate use of medication c. The patient should be able to request an early evaluation d. Any change in the efficacy of the maintenance dose requires a face to face encounter for assessment prior to modifying therapy	None	Reviewed, Deleted	
3	K3	4	Monthly renewal of the prescription for opioid medication can be facilitated by: a. Phone call, email, or mail-in requests; and/or b. A structured program (e.g., opioid renewal clinic) staffed by advanced care providers (e.g., pharmacists, nurse practitioners, PA-Cs, psychologists, RNs) with appropriate co-signatures	None	Not reviewed, Deleted	
3	K3	5	In addition to the maintenance opioid analgesic, supplemental doses of short-acting opioids may be considered. (See Annotation K4 – Supplemental Therapy)	None	Not reviewed, Deleted	
3	K3	6	Assess and re-educate patient's adherence with safely storing opioid medications.	None	Not reviewed, Deleted	
3	K4	1	Evaluate worsening or new pain symptoms to determine the cause and the best treatment approach.	None	Not reviewed, Deleted	
3	K4	2	Encourage the use of non-pharmacologic modalities (e.g., pacing activities, relaxation, heat, cognitive behavioral therapy).	None	Reviewed, New-replaced	Recommendation 1
3	K4	3	Carefully evaluate the potential benefits, side effects, and risks when considering supplemental opioids.	None	Not reviewed, Deleted	
3	K4	4	Consider supplemental short-acting opioid, non-opioid, or a combination of both agents on an as- needed basis.	None	Not reviewed, Deleted	
3	K4	5	Avoid the use of rapid-onset opioids as supplemental opioid therapy in chronic pain, unless the time course of action of the preparation matches the temporal pattern of pain intensity fluctuation.	None	Not reviewed, Deleted	

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Module	Section	Number				
3	K4	6	Avoid use of long-acting agents for acute pain or on an as-needed basis in an outpatient setting.	None	Not reviewed, Deleted	
3	K4	7	When using combination products, do not exceed maximum recommended daily doses of acetaminophen, aspirin, or ibuprofen.	None	Not reviewed, Deleted	
3	K4	8	Avoid the use of mixed agonist-antagonist opioids, as these agents may precipitate withdrawal in patients who have physical opioid dependence.	None	Not reviewed, Deleted	
3	K4	9	Whenever possible, use the same opioid for supplemental therapy as the long-acting opioid to avoid confusion about the cause of any adverse effects that may develop.	None	Not reviewed, Deleted	
3	K4	10	When using short-acting pure agonist opioids (alone or in combination with non-opioid analgesics) for supplemental therapy, give opioid doses equivalent to about 10-15%, the every four hourly equivalent, or 1/6th of the total daily opioid dose, as needed.	None	Not reviewed, Deleted	
3	K4	11	Use rescue short-acting opioids to assist with pain management during the titration process and to help determine the long-term daily opioid dose.	None	Not reviewed, Deleted	
3	K4	12	Do not use routinely for chronic pain. If necessary, use breakthrough pain therapy sparingly.	None	Not reviewed, Deleted	
3	K4	13	Consider adjusting the long-acting opioid regimen if pain exacerbations are interfering with patient function due to severity, frequency, or diurnal variations in pain intensity.	None	Not reviewed, Deleted	
3	K4	14	Educate and reassure patient, emphasizing realistic expectations about limitations of chronic opioid therapy, the normal cyclic nature of chronic pain, and the importance of pacing activities.	None	Not reviewed, Deleted	
3	K4	15	Consider providing preemptive analgesia for preventing incident pain e.g., 8 to 12 doses per month of short-acting opioid preparation.	None	Not reviewed, Deleted	
3	L	1	When writing a prescription for opioid therapy, be certain to record the name of the drug, the strength, the number of dosage units (written numerically and in text) and how the drug is to be taken. (In the case of methadone, indicate on the prescription that it is for pain as opposed to detoxification).	None	Not reviewed, Deleted	
3	L	2	Follow local regulations.	None	Not reviewed, Deleted	

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4	M1	1	Evaluate patient for opioid adverse effects: constipation, nausea, vomiting, headache, dyspepsia, pruritus, dizziness, tiredness, dry mouth, sweating, hyperalgesia, sexual dysfunction, and sedation.	None	Not reviewed, Deleted	
4	M1	2	Many adverse effects spontaneously resolve with continued administration and development of tolerance. Consider individual levels of tolerability to different opioid agents.	None	Not reviewed, Deleted	
4	M1	3	If not already done, anticipate and consider preventive treatment for common adverse effects, particularly constipation and nausea.	None	Not reviewed, Deleted	
4	M1	4	Keep in mind that slowly titrating the opioid dose, modifying the dosage regimen, treating symptoms, and rotating the opioid agents may successfully treat most adverse effects.	None	Not reviewed, Deleted	
4	M1	5	Consider evaluation of possible drug-to-drug interactions with other medications that have been prescribed for the patient (see Appendix E: Drug Table E4 – Drug Interactions).	None	Not reviewed, Deleted	

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Module	Section	Number				
4	M2	1	At every visit and telephone contact for opioid renewal, assess and document adherence with appropriate use of opioid analgesics, and any evidence of misuse, abuse, or addiction. a. Evaluate how and when the patient is taking medication, use of other medications including nonprescription and herbal preparations, and use of alcohol and illicit drugs b. Screening aids such as random pill counts, adherence checklists, or instruments such as the Screener and Opioid Assessment for Patients with Pain (SOAPP), may be used to assist the provider in assessing adherence c. With patient consent, obtain a Urine Drug Test (UDT) before initiating opioid therapy trial and randomly at follow-up visits to confirm the appropriate use of opioids (See Annotation M3) d. Assess and document adherence to other components of the treatment plan, such as follow up with referrals, tests, and other therapies e. Assess patients for behaviors that are predictive of addiction including repeated minor variations in adherence that may indicate an increased likelihood of addiction or serious non-adherence f. Assess patient's adherence and reeducate regarding the importance of safely storing opioid medications g. Assess and document patient motivation and barriers to adherence	None	Reviewed, New-replaced	Recommendation 7 Recommendation 9
4	M2	2	Based on the clinical assessment the provider should determine whether aberrant behavior is present and respond with appropriate action.	None	Not reviewed, Deleted	
4	M2	3	If the clinician is not sure of the meaning of the behavior, more frequent clinic visits, addiction or mental health specialist consultations, or periodic drug screens might be employed.	None	Reviewed, New-replaced	Recommendation 7 Recommendation 9
4	M2	4	When aberrant behaviors are present, providers should not stigmatize or judge patients but instead simply inform the individual that the behavior is unsafe and needs evaluation and adjustment in treatment through increased structure and monitoring or referral.	None	Not reviewed, Deleted	
4	M2	5	A continuing pattern of repeated episodes of non-adherence following treatment changes designed to maximize adherence should increase prescriber concerns and consideration of potential cessation of opioid therapy.	None	Reviewed, New-replaced	Recommendation 9

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Module	Section	Number				
4	M2	6	Consider involving family members or significant others in identifying solutions to non-adherence and in monitoring future adherence when possible. This may include a change in the patient's living situation that would provide greater structure (e.g., nursing home, assisted living facility), potentially enhance compliance, and reduce nonadherence	None	Not reviewed, Deleted	
4	M3	1	Inform patients that drug testing is a routine procedure for all patients starting or on opioid therapy, and is an important tool for monitoring the safety of their treatment.	None	Reviewed, New-replaced	Recommendation 7
4	M3	2	With patient consent, obtain a UDT in all patients prior to initiation of OT. [B]	B	Reviewed, New-replaced	Recommendation 7
4	M3	3	With patient consent monitor all patients on OT with periodic random UDTs to confirm adherence to the treatment plan. Increase the frequency of UDTs based on risk level for aberrant drug-related behaviors and following each dose increase. [B]	B	Reviewed, New-replaced	Recommendation 7
4	M3	4	Take into consideration a patient's refusal to take a UDT as part of the ongoing assessment of the patient's ability to adhere to the treatment plan and the level of risk for adverse outcomes (see Annotation F).	None	Not reviewed, Deleted	
4	M3	5	When interpreting UDT results take into account other clinical information (e.g., past SUD, other risk factors, aberrant drug-related behaviors, and other conditions indicating risk.)	None	Not reviewed, Deleted	
4	M3	6	Understanding of lab methods for drug testing and reporting are necessary to interpret UDT results (i.e., screen versus confirmatory test, substances tested, cut-off levels for tests). Maintain a close working relationship with the clinical laboratory to answer any questions about the UDT or for confirming the results.	None	Not reviewed, Deleted	

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Module	Section	Number				
4	M4	1	Evaluate and assess the patient for the following problems or other indications for consultation or referral: a. Patient with complex pain conditions b. Patient with significant medical comorbidities that may negatively impact opioid therapy c. Patient with significant concurrent psychiatric illnesses d. Patient who is unable to tolerate increased pain or physical withdrawal symptoms arising from opioid tapering when OT is being discontinued e. Opioid induced hyperalgesia or opioid tolerance suspected (i.e., pain increases or changes while on chronic stable opioid dosing and with an unchanged underlying medical condition causing the pain) f. Patient with conditions requiring management beyond the expertise level of the primary provider	None	Not reviewed, Deleted	
4	M5	1	Evaluate pain intensity at each visit. a. Intensity of pain should be measured in the following manner using a Numeric Rating Scale (NSR) (0 to 10) and include the following: • Current pain • Least pain in last week • "Usual" or "Average" pain in the last week b. The patient's response to current pain medications should be assessed each visit using questions such as: • "What is your intensity of pain after taking your current treatment/medication?" • "How long does your pain relief last after taking your medication?"	None	Not reviewed, Deleted	

2010 Recommendation Location[19]			2010 Recommendation Text[20]	2010 Grade[21]	Category[22]	2016 Recommendation (if applicable)[23]
Module	Section	Number				
4	M5	2	Evaluate pain-related function using objective documentation whenever possible, such as physical therapy progress notes, employment records, exercise diaries, family reports, clinician observations (e.g., walking distance), or validated instruments or NRS rating scales on a monthly basis during the titration phase and every six months after the patient is on stable opioids. Assessment of function may include: • Employment • Enjoyment of life • Emotional distress (depression and anxiety) • Housework, chores, hobbies, and other day to day activities • Sleep • Mobility • Self-care behaviors • Sexual function	None	Not reviewed, Deleted	
4	M5	3	Assess overall patient satisfaction with pain therapy at each visit	None	Not reviewed, Deleted	
4	M5	4	Emphasis should be given to capitalizing on improved analgesia by gains in physical and social function; opioid therapy should be considered complementary to other analgesic and rehabilitative approaches.	None	Not reviewed, Deleted	
5	N1	1	Adverse effects can usually be minimized through the use of low starting doses, slow titration rates, prophylactic and symptomatic treatments, and specific patient education provided at initiation of therapy.	None	Not reviewed, Deleted	
5	N1	2	Symptomatic treatment should be augmented with slow dosage titration, dose modification, and/or opioid rotation to minimize the adverse effects as follows: a. Titrate slowly, temporarily reducing or holding doses if necessary, or modify the dosage regimen to allow the patient to develop tolerance to the adverse effects b. If these measures fail to minimize the adverse effects, consider rotating to another opioid agent	None	Not reviewed, Deleted	
5	N1	3	If adverse effects are unmanageable and therapy is a greater detriment than benefit as determined by discussion with the patient and family, opioid therapy should be discontinued.	None	Not reviewed, Deleted	

2010 Recommendation Location[19]			2010 Recommendation Text[20]	2010 Grade[21]	Category[22]	2016 Recommendation (if applicable)[23]
Module	Section	Number				
5	N1	4	Initial bowel regimens should generally consist of a bowel stimulant and a stool softener as well as general measures, such as increased fluid intake, increased dietary fiber, and adequate exercise.	None	Not reviewed, Deleted	
5	N1	5	Routinely initiate a stimulant-based bowel regimen at commencement of chronic opioid therapy.	None	Not reviewed, Deleted	
5	N1	6	If the initial regimen is inadequate, mild hyperosmotic, saline, and emollient laxatives may be added.	None	Not reviewed, Deleted	
5	N1	7	If possible, reduce or discontinue other drugs that may cause or contribute to constipation.	None	Not reviewed, Deleted	
5	N1	8	Bulk-producing laxatives, such as psyllium and polycarbophil, are not recommended and are relatively contraindicated as they may exacerbate constipation and lead to intestinal obstruction in patients with poor fluid intake.	None	Not reviewed, Deleted	
5	N1	9	Assess patients for constipation symptoms at every office visit.	None	Not reviewed, Deleted	
5	N1	10	Consider prophylactic antiemetic therapy at initiation of therapy.	None	Not reviewed, Deleted	
5	N1	11	Rule out other causes of nausea, and/or treat based on cause including a. Stimulation of chemoreceptor trigger zone: dopamine or serotonin antagonist b. Slowed GI motility: metoclopramide c. Nausea associated with motion: dimenhydrinate or scopolamine.	None	Not reviewed, Deleted	
5	N1	12	Rule out an allergic reaction.	None	Not reviewed, Deleted	
5	N1	13	Itching may resolve spontaneously despite continuation of opioid therapy. If the itching does not spontaneously resolve, consider treatment with antihistamines.	None	Not reviewed, Deleted	
5	N1	14	Rule out other causes.	None	Not reviewed, Deleted	
5	N1	15	Reduce dose (with or without addition of a co-analgesic). Excessive sedation within the first few days of initiating opioids may require temporarily holding one or two doses and restarting at a lower dose to prevent respiratory depression.	None	Not reviewed, Deleted	

2010 Recommendation Location[19]			2010 Recommendation Text[20]	2010 Grade[21]	Category[22]	2016 Recommendation (if applicable)[23]
Module	Section	Number				
5	N1	16	Add or increase non-opioid or non-sedating adjuvant for additional pain relief so that the opioid can be reduced.	None	Not reviewed, Deleted	
5	N1	17	If the above measures fail to relieve sedation adequately, consider rotating to another opioid agent.	None	Not reviewed, Deleted	
5	N1	18	Consider adding caffeine or a prescription psychostimulant medication.	None	Not reviewed, Deleted	
5	N1	19	Rule out other causes.	None	Not reviewed, Deleted	
5	N1	20	Consider reducing or stopping (tapering) the dose.	None	Not reviewed, Deleted	
5	N1	21	Add or increase non-opioid or non-sedating adjuvant for additional pain relief so that the opioid can be reduced.	None	Not reviewed, Deleted	
5	N1	22	Rotate opioid agent.	None	Not reviewed, Deleted	
5	N1	23	If patient continues to deteriorate during titration phase and presents with symptoms of delirium, opioid therapy should be discontinued.	None	Not reviewed, Deleted	
5	N1	24	If patient develops increased confusion or major cognitive changes (delirium) during the maintenance phase, consider hospitalization to investigate the cause and to continue treatment safely.	None	Not reviewed, Deleted	
5	N1	25	Ask all patients on opioids for chronic pain about symptoms of opioid-induced endocrinopathy (i.e. hypogonadism) on each visit.	None	Not reviewed, Deleted	
5	N1	26	If opioid-induced endocrinopathy symptoms are present, , and not accounted for by another disorder or illness (e.g., depression, chronic disease), laboratory evaluation and consultation with an endocrinologist should be considered	None	Not reviewed, Deleted	
5	N1	27	Insufficient data exists to recommend routine laboratory screening for endocrinopathy in asymptomatic patients on OT.	None	Not reviewed, Deleted	
5	N1	28	There is insufficient evidence to make recommendations regarding OT and immune dysfunction.	None	Not reviewed, Deleted	

2010 Recommendation Location[19]			2010 Recommendation Text[20]	2010 Grade[21]	Category[22]	2016 Recommendation (if applicable)[23]
Module	Section	Number				
5	N1	29	Consider monitoring bone density in patients at risk for osteoporosis (See Table 6: Risk Factors for Osteoporosis), as patients with fractures associated with hypogonadism often have no other symptoms associated with hypogonadism.	None	Not reviewed, Deleted	
5	N2	1	If a medication causes unmanageable adverse effects, consider changing to an alternate opioid medication.	None	Not reviewed, Deleted	
5	N2	2	When therapy is a greater detriment than benefit as determined in consultation with the patient and family, opioid therapy should be discontinued.	None	Not reviewed, Deleted	
5	N3	1	Address safety issues immediately and apply legal mandates as appropriate.	None	Not reviewed, Deleted	
5	N3	2	Dangerous or illegal behaviors may require immediate cessation of the opioid therapy with consideration of appropriate treatment of potential withdrawal symptoms.	None	Not reviewed, Deleted	
5	N3	3	Document and refer to behavior health specialty those patients demonstrating behaviors suggestive of suicide.	None	Reviewed, Amended	Recommendation 8
5	N3	4	For a patient with evidence of diversion or dangerous or suicidal behavior the clinician should discontinue OT, refer as appropriate for emergency psychiatric evaluation, and flag the chart.	None	Not reviewed, Deleted	
5	N3	5	Consider notifying law enforcement about suspected criminal behaviors such as prescription fraud or diversion. Consult with counsel prior to doing so to clarify current confidentiality laws and regulations (e.g., VA /military police, risk manager, and/or regional counsel).	None	Not reviewed, Deleted	
5	N3	6	Carefully document the details of the situation in the clinical record, or not, as advised by risk management and/or legal counsel.	None	Not reviewed, Deleted	

2010 Recommendation Location[19]			2010 Recommendation Text[20]	2010 Grade[21]	Category[22]	2016 Recommendation (if applicable)[23]
Module	Section	Number				
5	N4	1	Consider adjustment of the initial treatment agreement, with emphasis upon specific adherence issues that have been identified; a more structured approach may be required. Possible responses to minor nonadherence might include: a. Reviewing, discussing, and restating the treatment plan b. Reviewing the written opioid treatment agreement and incorporating any needed revisions c. Recommending consultation with a pain, addictions, or behavior health specialist d. Administration of medications under supervision or with the assistance of others e. Change of medication, medication dose, or amount dispensed f. More frequent clinic contacts (telephonic, physician extenders, or clinic visits) g. Instituting periodic or random urine toxicology screens	None	Reviewed, New-replaced	Recommendation 9
5	N4	2	Consider setting up a grievance procedure with the patient.	None	Not reviewed, Deleted	
5	N4	3	Consider involving family members or significant others in identifying solutions to non-adherence and in monitoring future adherence when possible. This may include change in the patient's living situation that would provide greater structure (e.g. nursing home, assisted living facility) and might enhance compliance and reduce nonadherence.	None	Not reviewed, Deleted	
5	N5	1	Consider consultation with, or referral to, a behavioral health specialist if exacerbation of an underlying psychotic disorder is an issue, if the nonadherent behaviors may be due to changes in mood or increased suicidality, or if there is evidence of increased and poorly controlled anger and tendency to violent behaviors (see Annotation O2).	None	Not reviewed, Deleted	
5	N5	2	Consider referral to an addiction specialist if the nonadherent behaviors are those associated with possible addiction (see Annotation O1).	None	Reviewed, New-replaced	Recommendation 16
5	N5	3	Patients presenting with persistent or troublesome aberrant behavior who do not respond to intervention by primary care should be referred for evaluation and management of OT to a more structured care environment (e.g., Pharmacy Pain Management Clinic / Opioid Renewal Pain Care Clinic/ Pain Medicine Clinic).	None	Reviewed, New-replaced	Recommendation 16
5	N5	4	If such programs are not available, consider continuing OT with increased frequency of monitoring and screening, performing a comprehensive behavioral assessment, and addressing co-morbidities.	None	Reviewed, New-replaced	Recommendation 16

2010 Recommendation Location[19]			2010 Recommendation Text[20]	2010 Grade[21]	Category[22]	2016 Recommendation (if applicable)[23]
Module	Section	Number				
6	O1	1	Consider consultation or referral to addiction specialty for evaluation and treatment in the following conditions: a. Demonstration of behaviors suggesting addiction to prescribed opioids or substance use disorders b. Patients with a significant chronic, or substantiated pain, who develop addiction behaviors in the context of chronic opioid therapy c. Uncontrolled substance use disorder (excluding nicotine) d. Behaviors characteristic of compulsive drug use (addiction) to either opioids or other drugs or alcohol should be referred to an addiction specialty e. Complex conditions who manifest behaviors characteristic of addiction with multiple co- occurring psychiatric disorders f. Need for tapering of opioids or unable to tolerate tapering after discontinuation of OT.	None	Reviewed, New-Replaced	Recommendation 16
6	O1	2	Consider consultation with a SUD specialist to evaluate the risk of recurrent substance abuse or to assist with ongoing management.	None	Reviewed, New-replaced	Recommendation 17
6	O1	3	Refer patient for psychosocial treatments specific to prescription medication addiction/abuse. These can include addiction counselors comfortable with such topics, and self-help organizations (Pills Anonymous/PA, the National Chronic Pain Outreach association, and other similar organizations).	None	Not reviewed, Deleted	
6	O2	1	Consider referral to a Pain Medicine Specialist in the following situations: a. Patient with complex pain conditions or polytrauma b. Patient with significant medical comorbidities that may negatively impact opioid therapy c. Patient who is unable to tolerate increased pain or physical withdrawal symptoms arising from opioid tapering when OT is being discontinued d. Opioid induced hyperalgesia or opioid tolerance is suspected e. High dose of medication (greater than 200 mg/day morphine equivalent) provides no further improvement in function f. Patient requiring management beyond the expertise of the primary provider	None	Not reviewed, Deleted	

2010 Recommendation Location[19]			2010 Recommendation Text[20]	2010 Grade[21]	Category[22]	2016 Recommendation (if applicable)[23]
Module	Section	Number				
6	O2	2	Consider Referral to/consultation with a Behavioral Health Provider for evaluation and treatment in the following conditions: a. Exacerbation of an underlying psychotic disorder b. Uncontrolled, severe psychiatric disorder or those who are emotionally unstable c. Demonstration of high-risk behaviors suggestive of suicide ideation d. Psychosocial problems or comorbidities that may benefit from disease or case management e. Adverse behavioral or cognitive effects of OT f. Co-occurring trauma related conditions (mTBI, TBI, PTSD)	None	Not reviewed, Deleted	
7	P	1	Schedule follow-up visits at least every 2-4 weeks after any change in medication regimen and at least once every 1-6 months for the duration of the therapy (maintenance).	None	Not reviewed, Deleted	
7	P	2	Assess at each visit: a. Comfort (degree of analgesia) b. Opioid-related adverse effects c. Functional status (physical and psychosocial) d. Adherence to opioid treatment agreement and other aspects of treatment plan e. Obtain laboratory studies (especially liver or kidney function screens), and/or order drug screens as indicated f. Use of self-report instruments (diary, opioid log) may be helpful but should not be required.	None	Not reviewed, Deleted	
7	P	3	Documentation is essential and the medical record for each encounter should specifically address comfort, function, adverse-effects, and treatment plan adherence.	None	Not reviewed, Deleted	
8	Q	1	Opioid therapy should be tapered off and discontinued if any of the following situations occur: a. The medication fails to show partial analgesia with incremental dose titration b. Trials with different agents provide inadequate analgesia c. There is other evidence that the pain may not be opioid responsive d. Real or potential harms outweigh real or potential benefits e. Patient request.	None	Not reviewed, Deleted	
8	Q	2	Consider decreasing the opioid dose when pain level decreases in stable patients. (See Annotation X – Tapering)	None	Not reviewed, Deleted	

2010 Recommendation Location[19]			2010 Recommendation Text[20]	2010 Grade[21]	Category[22]	2016 Recommendation (if applicable)[23]
Module	Section	Number				
8	R	1	Document, and offer referral to addiction specialty for patients demonstrating behaviors suggesting addiction to prescribed opioids or substance use disorders.	None	Reviewed, New-replaced	Recommendation 17
8	R	2	Discuss pharmacotherapy options with all patients with opioid and/or alcohol dependence.	None	Reviewed, New-replaced	Recommendation 17
8	R	3	If there are clearly unsafe or illegal behaviors, opioid prescribing should stop immediately and withdrawal should be addressed.	None	Not reviewed, Deleted	
8	S	1	Attempt to maintain contact with any patient who withdraws from treatment due to a disagreement.	None	Not reviewed, Deleted	
8	S	2	Refer patients with comorbid psychiatric disorders to appropriate mental health providers.	None	Not reviewed, Deleted	
8	S	3	Identify and document any co-occurring disorders (CODs) in patients with substance use disorders; a. Psychiatric history, including symptoms and their relation to substance use, current and past diagnoses, treatments and providers b. Infectious diseases (HIV, Hepatitis C, sexually transmitted disease) c. For patients using nicotine offer and recommend tobacco use cessation treatment d. Medical CODs that may be related to or affected by substance use (e.g., diabetes, cardiovascular disease, digestive disorders, skin infections, respiratory disorders, dementia, cerebrovascular disease)	None	Not reviewed, Deleted	
8	S	4	Individuals with SUD should be assessed for any significant, unmet psychosocial needs or situational stressors. These include but are not limited to: a. Inadequate or no housing b. Financial difficulties, especially if unable to meet basic needs c. Problematic family relationships or situations (including caregiver burden or domestic violence) d. Poor social support e. Religious and spiritual problems f. Occupational problems g. Difficulties with activities of daily living or instrumental activities of daily living	None	Not reviewed, Deleted	
8	T	1	Decisions regarding tapering schedule should be made on an individual basis. Sometimes faster or slower tapering may be warranted.	None	Not reviewed, Deleted	

2010 Recommendation Location[19]			2010 Recommendation Text[20]	2010 Grade[21]	Category[22]	2016 Recommendation (if applicable)[23]
Module	Section	Number				
8	T	2	For those patients who are at high risk of aberrant behaviors (parasuicidal acts, dealing/selling medications, or those with severe impulse control disorders), tapering opioid in a primary care setting is not appropriate and those patients should be referred to an addiction or pain specialist with expertise dealing with difficult cases.	None	Not reviewed, Deleted	
8	T	3	Patients with complicated withdrawal symptoms should be referred to a pain specialist or a center specializing in withdrawal treatment.	None	Not reviewed, Deleted	
8	T	4	Patient being tapered due to development of addiction should be referred for SUD treatment. Opioid detoxification in a primary care setting followed by ongoing substance use treatment may be appropriate.	None	Not reviewed, Deleted	
8	U	1	Complete evaluation of treatment, comorbidity, psychological condition, and other relevant factors should be completed prior to the initiation of the taper.	None	Not reviewed, Deleted	
8	U	2	Clear written and verbal instructions should be given to patients/family to educate them about the slow taper protocol that will minimize abstinence (withdrawal) syndromes.	None	Not reviewed, Deleted	
8	U	3	Patients who are unable to tolerate the taper as described should be considered for referral to, or consultation with, a pain specialist, substance use specialist or other expert.	None	Not reviewed, Deleted	
8	U	4	Withdrawal management for addicted patients is not part of this guideline. Refer to the VA/DoD Guideline for the Management of Substance Use Disorders.	None	Not reviewed, Deleted	
8	V	1	Do not abandon a patient under any circumstances.	None	Not reviewed, Deleted	
8	V	2	Maintain contact with any patient who withdraws from treatment due to a disagreement.	None	Not reviewed, Deleted	
8	V	3	Refer patients with comorbid psychiatric disorders to appropriate mental health providers.	None	Not reviewed, Deleted	
9	W	1	Use caution when using opioids in patients with history of substance use disorders. [B]	B	Reviewed, Deleted	
9	W	2	Use an integrated treatment approach addressing both pain [B] and SUD issues with appropriate information sharing. [C]	C	Not reviewed, Deleted	

2010 Recommendation Location[19]			2010 Recommendation Text[20]	2010 Grade[21]	Category[22]	2016 Recommendation (if applicable)[23]
Module	Section	Number				
9	W	3	Patients on opioid agonist therapy for DSM-IV diagnosis of opioid dependence who have a co- occurring chronic pain disorder should be treated for pain considering the following options: a. Use non-pharmacologic interventions b. Use other non-opioid pharmacologic treatment modalities c. Cautious use of opioid therapy by using another opioid agonist with slow titration and careful communication with the SUD opioid agonist therapy prescribers. [B]	B	Reviewed, Deleted	
9	W	4	Perform urine drug testing as an adjunctive tool at regular intervals. [B]	B	Reviewed, New-replaced	Recommendation 9
9	W	5	Management of OT in patients on sublingual (SL) buprenorphine (with or without naloxone) for DSM-IV diagnosis of opioid dependence: a. SL buprenorphine is FDA-approved for treatment of opioid dependence and can only be prescribed by a qualified and DEA-waivered physician for this purpose b. Patients on SL buprenorphine should not receive full agonist opioids concomitantly for routine pain control c. Nonopioid and nonpharmacologic strategies for pain management should be maximized In the event of anticipated pain (i.e., an elective procedure or surgery) SL buprenorphine should be stopped for 48 hr before the scheduled event e. For unanticipated pain (trauma, emergency surgery or procedure) the care team managing the acute pain should be notified that the patient is prescribed SL buprenorphine and when the last dose was taken.	None	Not reviewed, Deleted	
9	X	1	Be vigilant for sleep apnea during OT. If clinical suspicion exists for the presence of sleep apnea in a patient on OT, sleep study should be considered. [B].	B	Not reviewed, Deleted	

2010 Recommendation Location[19]			2010 Recommendation Text[20]	2010 Grade[21]	Category[22]	2016 Recommendation (if applicable)[23]
Module	Section	Number				
9	X	2	Patients on OT who present with sleep disorder confirmed by a sleep study should be assessed for the appropriateness of continuing OT and should be evaluated for the risks (based on the severity of the sleep-disordered breathing) versus benefits of OT. If OT is continued, it should be titrated cautiously. Patients found to have sleep-disordered breathing should be followed with a repeated sleep study. [C]	C	Not reviewed, Deleted	
9	X	3	Patient with abnormal sleep study should be educated about the significant additional risks including breathing disruption, and instructed to avoid alcohol, or any CNS-depressant medication. [A]	A	Not reviewed, Deleted	
9	X	4	The type of sleep apnea should be evaluated to determine if it is obstructive or central. CPAP may worsen central sleep apnea. [D]	D	Not reviewed, Deleted	
9	X	5	Patients with sleep apnea who are on OT may benefit from a reduction in the dose of their opioids.	None	Not reviewed, Deleted	
9	X	6	Discontinuation of opioid therapy should be considered if the sleep apnea is severe or life threatening.	None	Not reviewed, Deleted	
9	X	7	Consider more careful monitoring of OT in patients treated with methadone and/or benzodiazepines. [B]	B	Not reviewed, Deleted	

Appendix I: Participant List

Elizabeth (Liz) Rees Atayde, RN, MSN, FNP, CCM, CPHM Nursing, Medical Management Medical Management Consultant/CPG Coordinator U.S. Army Medical Command Fort Sam Houston, TX	LTC Robert Brutcher, PharmD, PhD Pharmacy Deputy Director, Department of Pharmacy Walter Reed National Military Medical Center/ Defense Health Agency Bethesda, MD
Michael O. Chaffman, PharmD, BCPS Pharmacy National PBM Clinical Pharmacy Program Manager, Veterans Health Administration Pharmacy Benefits Management Services Hines, IL	Corinne K. B. Devlin, MSN, RN, FNP-BC Family Nurse Practitioner Chief, Office of Evidence Based Practice U.S. Army Medical Command Clinical Performance Assurance Directorate Fort Sam Houston, TX
Karen Drexler, MD Substance Use Disorders, Psychiatry National Mental Health Program Director, Substance Use Disorders Mental Health Services, VA Central Office Atlanta, GA	LTC William Grief, MD Family Medicine, Pain Medicine Chief, Department of Pain Management Madigan Army Medical Center Joint Base Lewis-McChord, WA
James Hardin, LCSW-C, MAC Social Work Chief, Addiction Treatment Services Walter Reed National Military Medical Center Bethesda, MD	Connie Kurihara, RN Pain Management Research Nurse Walter Reed National Military Medical Center Bethesda, MD
Franz Macedo, DO Pain Medicine, Physical Medicine and Rehabilitation Medical Director, Comprehensive Pain Center Minneapolis VA Medical Center Minneapolis, MN	Aram Mardian, MD Family Medicine, Primary Care Chief, Chronic Pain Wellness Program Phoenix VA Health Care System Phoenix, AZ
Anthony J. Mariano, PhD Pain Psychology Director, Pain Psychology, VISN 20 Pain Medicine and Functional Rehabilitation Center VA Puget Sound Healthcare System Seattle, WA	CDR Marisol Martinez, PharmD, MBA Pharmacy Clinical Pharmacy Analyst U.S. Public Health Service Defense Health Agency Pharmacy Operations Division San Antonio, TX
Capt Erick C. Messler, PhD Psychology Director of Psychological Health Malmstrom Air Force Base, MT	Ilene Robeck, MD Internal Medicine, Addiction Medicine, Mental/Behavioral Health Co-Chair, National Primary Care Pain Champions Initiative Director of Virtual Pain Care, Richmond VA Medical Center Richmond, VA

Jack Rosenberg, MD, FASAM (Champion) Pain Medicine, Anesthesiology, Addiction Chair, National Pain Guidelines Group Member, National Pain Management Strategy Coordinating Committee Co-Physician Pain Lead, VISN 10 Staff Physician, Ann Arbor VA Medical Center Ann Arbor, MI	Friedhelm Sandbrink, MD Pain Medicine, Neurology, Clinical Neurophysiology Chief, Pain Management Program, Department of Neurology, Washington DC VA Medical Center Deputy National Program Director for Pain Management, Specialty Care Services, VHA Washington, DC
LTC Jason Silvernail DPT, DSc, FAAOMPT Physical Therapy Chief, Physical Therapy Service Walter Reed National Military Medical Center/ Defense Health Agency Bethesda, MD	Maria Silveira, MD, MA, MPH Palliative Care, Geriatrics Clinical Scientist, Geriatric Research Education Clinical Center, Ann Arbor VA Medical Center Ann Arbor, MI
Christopher Spevak, MD, MPH, JD (Champion) Pain Medicine, Addiction Medicine Director, Prescription Medication Misuse Program Deputy Director, Wounded Warrior and NCRP Initiatives Walter Reed National Military Medical Center/ Defense Health Agency Bethesda, MD	Nancy Wiedemer, MSN, RN, ANP-BC Nursing, Primary Care, Pain Medicine Pain Management and Opioid Safety Lead for VISN 4 Pain Management Coordinator, Corporal Michael Crescenz VA Medical Center, Philadelphia
CAPT Necia Williams, MD Pain Medicine, Anesthesiology Command Surgeon Marine Special Operations Command Camp Lejeune, NC	

Appendix J: Literature Review Search Terms and Strategy

A. Topic-specific Search Terms

The search strategies employed combinations of free-text keywords as well as controlled vocabulary terms including (but not limited to) the following concepts. Strategies for each bibliographic database follow this table.

Table J-1. EMTREE, Medical Subject Headings (MeSH), PsycInfo, and Keywords

Concept	Controlled Vocabulary	Keywords
Patient population		
Chronic Pain	**EMBASE** 'chronic disease'/exp 'chronic inflammatory pain'/exp 'chronic pain' 'pain'/exp **MeSH** exp chronic disease/ exp pain/ **PsycINFO** Exp chronic illness/ exp chronic pain/ exp pain/	chronic Chronic adj3 pain* Chronic NEXT/3 pain* Long?term NEXT/3 pain* months pain weeks year*
Chronic Opioid Use	**EMBASE** 'analgesic agent'/exp 'codeine'/de 'drug therapy'/lnk 'fentanyl'/de 'morphine'/de 'narcotic agent'/exp 'narcotics'/exp 'narcotic drugs'/exp 'opiate'/de 'opiates'/exp **MeSH** Chronic pain/drug therapy exp analgesics, opioids exp narcotics **PsycINFO** exp analgesic drugs exp narcotics exp narcotic drugs exp opiates	Analgesic* COT 'chronic NEXT/1 opi* NEXT/1 therapy' 'chronic opi* therapy' codeine Fentanyl heroin Hydrocodone Hydromorphone Long?term Methadone months morphine narcotic* Opi* Oxycodone Oxycontin Oxymorphone percocet Tapentadol Tramadol Vicodin weeks Year*

Concept	Controlled Vocabulary	Keywords
KQ 1 **Contraindications** What is the evidence that the following medical or mental health conditions are absolute or relative contraindications of prescribing LOT? ■ Active pursuit of compensation ■ Centralized pain conditions such as fibromyalgia ■ Chronic obstructive pulmonary disease ■ Cognitive impairment ■ Depression ■ Headache ■ GI motility problems (e.g., toxic megacolon, GI pain syndromes, narcotic bowel syndrome) ■ Immune status changes ■ Inability to participate in comprehensive treatment plan ■ Incarceration (history of) ■ Hepatic, renal, or pulmonary disease ■ Suspected opioid misuse (e.g., overdose, early refills, diversion, taking more than prescribed) ■ Osteoporosis ■ Personality disorders ■ Posttraumatic stress disorder ■ Sleep disorders ■ SUD (current or history of)—include specific disorders and appropriate key words in search ■ Suicidality ■ Traumatic brain injury ■ Use of medical marijuana ■ QT prolongation	**EMBASE** 'drug contraindication'/exp 'drug interaction'/exp 'drug safety'/exp **MeSH** analgesics, opioid/contraindications Polypharmacy/ **PsycINFO** Drug interactions/ Polypharmacy/ Safety/	Cardiovascular CNS COPD Compensation* Contraindication* depression Fibromyalgia gastrointestinal Headache* Heart immune Liver Lung Obstructive Osteoporosis (personality or cognitive or mental or neuro*) adj3 (disorder* or disease* or illness*)) Post?traumatic stress PTSD Respiratory Sleep Substance adj2 (abuse OR misuse) Substance use disorder SUD Suicide suicidality TBI Traumatic brain

Concept	Controlled Vocabulary	Keywords
KQ 2 **Risk factors for the continuum of misuse or OUD** What factors increase the risk of developing misuse or OUD when considering LTOT? a) What are the risks for long-term use associated with acute use of opioids in treating acute pain?	**EMBASE** 'analgesic agent abuse'/exp 'bullying'/exp 'opiate addiction'/exp 'opioid-related disorders'/exp 'risk'/exp 'sexual abuse'/exp **MeSH** 'bullying'/ 'domestic violence'/exp 'risk assessment'/exp 'substance-related disorders'/exp **PsycINFO** Exp addiction/ Exp at risk populations/ Exp codependency/ Exp drug abuse/ Exp drug addiction/ Exp drug overdoses/ Exp illegal drug distribution/ Exp risk assessment/ Exp risk factors Exp risk perception/	Abuse Acute Addict* Assess* Bully Bullying Day* dependency Disorder* Early Initial New New onset Overdose* Predict* Risk* Short term violence

Concept	Controlled Vocabulary	Keywords
KQ 3 AND KQ 4 **Effectiveness of LTOT** What is the comparative effectiveness of LTOT versus other treatment modalities? a) What is the comparative effectiveness of LTOT versus other treatment modalities for patients with a history of or current SUD? b) What is the effectiveness of non-pharmacological interventions in patients with chronic pain? **Safety of LTOT** What is the safety of LTOT versus other treatment modalities? a) What is the safety of LTOT versus other treatment modalities for patients with a history of or current SUD? b) What is the safety of non-pharmacological interventions in patients with chronic pain?	**EMBASE** 'adverse drug events'/exp 'adverse drug reaction'/exp 'adverse drug reaction'/lnk 'drug overdose'/exp 'patient safety'/exp 'prescription drugs'/exp 'side effect'/lnk 'side effect'/de 'treatment outcome'/de **MeSH** 'analgesics, opioid'/*adverse effects 'prescription drugs'/adverse effects 'quality of life' 'risk' 'side effect'/de 'treatment outcome' **PsycINFO** *quality of life/ "side effects (drug)"/ *treatment outcomes/ Drug overdose/*prevention & control	Aberrant NEXT/3 behavior* Absence absent Abuse Accident* 'ade' Addict* adverse 'adverse drug events' Adverse NEXT/1 effect* Anxiety cardiac cardiovascular cognitive complication depression Disorder* Diversion effective effectiveness Fall Falls Harm* Misuse Mood Outcome* Overdose* 'pain relief' Pain NEXT/2 relief Pain NEXT/3 reliev* poison* 'quality of life' QOL Safety 'side effect*' Sleep s

Concept	Controlled Vocabulary	Keywords
KQ 5 **Effectiveness of different opioid formulations** What is the comparative effectiveness and safety of various opioid formulations? a) Immediate-release/short-acting opioids compared to ER/long-acting opioids b) Route of administration/ delivery alternatives such as transdermal, buccal, sublingual, pumps c) Abuse deterrent formulations compared to non-abuse deterrent formulations d) Tramadol and other dual-mechanism opioids e) Buprenorphine f) Methadone	**EMBASE** 'short acting analgesic agent'/exp **MeSH** 'analgesics, short-acting' **PsycINFO** *drug therapy	Abuse-deterrent controlled 'controlled release' extended 'extended release' Formulation immediate 'immediate release' LA 'long?acting' Medication Medicine Pill* Prescription* SA 'short?acting' (short* OR long* OR immediate OR extended OR controlled OR sustained AND (release* OR act*)) Sustained

Concept	Controlled Vocabulary	Keywords
KQ 6 **Added benzodiazepines** Does additional use of benzodiazepines or other psychoactive medications increase the risk of adverse events compared to OT alone?	**EMBASE** 'antidepressant agent'/exp 'benzodiazepine' 'benzodiazepine derivative'/exp 'hypnotic sedative agent'/exp 'narcotic analgesic agent'/exp 'non prescription drug' 'prescription drug' **MeSH** 'patient safety' 'polypharmacy'/exp 'safety' **PsycINFO** exp analgesic drugs/ Exp anesthetic drugs/ Exp anticonvulsive drugs/ Exp antidepressant drugs/ Exp antiemetic drugs/ Exp antihistaminic drugs/ Exp antihypertensive drugs/ exp benzodiazepines/ exp cns depressant drugs/ drug therapy/sh *hypnotic drugs/ Insomnia.id. Major depression.id. Exp polypharmacy/ Schizophrenia.id. Exp sedatives/ Exp self medication/	Ambien 'anti depressant' Antidepressant* Anti-depressant' Benzodiazepine* 'eszopiclone' Hypnotic* lunesta OTC 'over-the-counter' 'over the counter' prescription* polypharmacy psychoactive* sonata stimulant* 'z drug' 'z drugs' 'zaleplon' 'zolpidem'

Concept	Controlled Vocabulary	Keywords
KQ 7 **Risk mitigation strategies** What is the comparative effectiveness of different risk mitigation strategies for patients either on LTOT or being considered for LTOT? a) Does this differ for patients with history of or current SUD? b) Does this differ for patients with mental health comorbidities? c) Does this differ for patients with medical comorbidities? d) What is the safety and effectiveness of take-home naloxone kits?	**EMBASE** 'naloxone'/exp 'opiate addiction'/exp 'patient education'/exp 'prescription drug diversion'/exp 'risk reduction'/exp 'substance abuse'/exp 'urinalysis'/exp **MeSH** 'contracts' 'drug monitoring' exp 'patient compliance'/ exp 'risk'/ **PsycINFO** exp addiction/ Exp client education/ exp drug abuse/ drug abuse.sh. exp drug addiction/ opiates.id. exp monitoring/ exp naloxone/ exp patient compliance/ Exp prescription drugs/ Exp risk assessment/ Exp risk evaluation and mitigation strategy/ Exp risk perception/ Exp treatment compliance/ Exp urinalysis/	Abuse Addict* agreement 'call back' Call-back Compliance comply consent contract database diversion divert doctor Detect* Diversion Divert Misuse Mitigat* Monitor* naloxone Naloxone NEXT/2 rescue office Pill NEXT/2 count physician primary Precaution* Query Recall Rescue Risk* Risk NEXT/5 reduc* Risk NEXT/5 mitigat* Screen* surveillance Test* Urin*

Concept	Controlled Vocabulary	Keywords
KQ 8 **Treatment of OUD** What is the safety and effectiveness of treatment of OUD (diagnosed or suspected) in patients with chronic pain? a) Do outcomes vary by severity of OUD?	**EMBASE** 'acceptance and commitment therapy'/exp 'addiction'/exp 'analgesic agent abuse'/exp 'cognitive therapy'/exp 'drug abuse'/exp 'drug dependence'/exp 'narcotic analgesic agent'/exp 'narcotic dependence'/exp 'opiates'/exp 'opiate addiction'/exp 'psychotherapy'/exp 'support group'/exp **MeSH** 'analgesics, opioid'/exp 'cognitive therapy'/exp 'counseling'/exp 'motivational interviewing'/ 'narcotics'/exp 'substance abuse detection'/exp 'substance-related disorders'/exp **PsycINFO** exp addiction/ Exp adjunctive treatment/ Exp cognitive therapy/ Exp counseling/ exp drug abuse/ drug abuse.sh. exp drug addiction/ exp drug dependence/ electrosleep treatment/ exp motivational interviewing/ exp opiates/ opiates.id. Exp prescription drugs/ Exp psychotherapy/ Exp support group/ Exp treatment/ Exp treatment compliance/ Exp treatment effectiveness evaluation/ Exp treatment outcomes/	aberrant Abuse Addict* Behavioral buprenorphine Cognitive Contingency 'contingency management' Counsel* counseling drug interview* methadone misuse motivation* naltrexone therapy treat* treatment

Concept	Controlled Vocabulary	Keywords
KQ 9 **Tapering** What is the safety and effectiveness of different tapering strategies and schedules?	**EMBASE** 'analgesia'/exp 'clinical protocol'/exp 'dose response'/exp 'drug administration'.exp 'drug therapy'/lnk 'pain management'/exp **MeSH** 'clinical protocols'/exp 'drug administration schedule'/exp **PsycINFO** exp analgesic drugs/ Exp drug dosages/ Exp pain management/	Adjust* administration Decrease* Dose Dosing plan protocol Reduc* Schedule Strategy strategies Taper* Titrat*

B. Search Strategies

Table J-2. MEDLINE/PSYCINFO (presented in OVID syntax)

Set Number	Concept	Search Statement
1	Chronic pain	*exp chronic pain/ OR (exp pain/ AND (chronic OR long?term)) OR (exp chronic illness/ AND pain?)
2		Chronic adj3 pain?.ti,ab.
3	Combine	1 OR 2
4	LTOT	exp analgesic drugs/ or exp narcotics/ or exp narcotic drugs/ or exp opiates/
5		(opioid* or opiod* or opiate* or oposal or opon or narcotic*).mp. OR (morphine or codeine or fentanyl).mp.
6		(Oxymorphone or tapentadol or methadone or fentanyl or hydrocodone or oxycodone or codeine or morphine or hydromorphone or tramadol).mp.
7	Combine	4 OR 5 OR 6
8	Combine chronic pain and LTOT	3 AND 7
9	Contraindications (KQ1)	(Contraindication or COPD or cardiovascular or respiratory or obstructive or lung or fibromyalgia or headache or heart or liver or sleep or osteoporosis or CNS or immune or gastrointestinal).mp.
10		(medic* adj1 marijuana).mp. or ("post?traumatic stress" or PTSD).mp. or traumatic brain.mp. or TBI.ti,ab. or (substance adj2 abuse).mp. or (substance adj2 misuse).mp. or (depression or suicide or suicidality).mp. or ((personality or cognitive or mental or neuro*) adj3 (disorder* or disease* or illness*)).mp.
11		9 OR 10
12	Workers compensation	exp litigation/ or exp workers' compensation insurance/ or lawsuit.mp. or litigation.mp. exp insurance/ or insurance claim.mp. or exp disability evaluation/ or exp malingering/ or malingering.mp.
13		(worker adj2 compensation).mp. or litigation.ti. or lawsuit.ti. or claim*.ti. or disability*.ti. or compensation.ti. or malinger*.ti.
14	combine	11 OR 12 OR 13

Set Number	Concept	Search Statement
15	Combine with chronic pain and LTOT	8 AND 14
16	Risk of misuse (KQ2)	Exp drug abuse/ or exp addiction/ or exp codependency/ or exp drug addiction/ or exp drug overdoses/ or exp illegal drug distribution/
17		16 AND (opi* or narcotic* or hydrocodone or vicodin or oxycodone or oxycontin or percocet or heroin or methadone or morphine or codeine or analgesic*).mp.
18		((opi* or narcotic* or hydrocodone or vicodin or oxycodone or oxycontin or percocet or heroin or methadone or morphine or codeine or analgesic*) adj2 (addict* or abuse or misuse or disorder* or diversion)).mp.
19		Risk*.mp. or exp risk assessment/ or exp risk perception/ or exp at risk populations/ or exp risk factors/
20		17 OR 18
21	Combine risk and abuse	19 AND 20
22	Combine with chronic pain and LTOT	8 AND 21
23	Effectiveness and Safety of LTOT (KQs 3 and 4)	exp "Side Effects (Drug)"/ or exp "side effects (treatment)"/ or exp "complications (disorders)"/
24		exp Suicide/ or exp Major Depression/ or exp Attempted Suicide/ or exp Drug Abuse/ or exp Drug Overdoses/ or exp Drug Addiction/ or exp Safety/ or overdose.mp. or adverse events.mp. or drug addiction.mp.
25		Exp pain management/ or (pain adj2 (reliev* or relief)) or exp Quality of Life/ or quality of life.mp. or exp treatment outcomes/ or outcomes.mp.
26		((adverse adj1 event*) or (adverse adj1 effect*) or (aberrant adj3 behavior*)).mp. or (overdose* or diversion or addict* or abuse or accident* or complication* or absence or absent or falls or fall or depression or anxiety or mood or sleep or cardiovascular or cardiac or cognitive).ab,ti.
27		((work or occupation* or job) adj3 (injur* or accident or absence or performance)).mp. or exp safety/ or exp occupational safety/ or exp accidents/ or exp job performance/ or exp employee absenteeism/ or exp cognitive processes/ OR exp cognitive impairment/
28		exp driving behavior/ or exp drivers/ or exp risk taking/ or exp risk perception/ or exp highway safety/ or exp motor traffic accidents/ or exp motor vehicles/ or exp transportation accidents/ or exp motor traffic accidents/ or (accident* or crash or collison or wreck).mp. or ((drive or driving or car* or traffic or vehicle*) and (safe* or accident* or crash* or wreck* or impair* or risk* or collison*)).mp.
29	Combine	23 OR 24 OR 25 OR 26 OR 27 OR 28
30	Combine with LTOT	7 AND 29
31	Formulations (KQ5)	(*drug therapy/ or (prescription* or medication or medicine or pill*).mp. AND opi*
32		'immediate release' OR 'extended release' OR 'short acting' OR shortacting OR sa OR 'long acting' OR longacting OR la OR 'controlled release' OR (short* OR long* OR immediate OR extended OR controlled OR sustained AND (release* OR act*)).mp.
33		(formulation* or short?act* or long?act* or immediate or extended or controlled or sustained or abuse-deterrent or (abuse adj1 deterrent)).mp.

Set Number	Concept	Search Statement
34		(opiate* or opioid).ti. and (formulation* or short?act* or long?act* or immediate or extended or controlled or sustained).mp.
35	Combine	(31 AND (32 OR 33)) OR 34
36	Combine with LTOT	7 AND 35
37	Added benzodiazepines (KQ6)	benzodiazepine*.mp. or exp benzodiazepines/
38		*hypnotic drugs/ or exp analgesic drugs/ or exp anesthetic drugs/ or exp anticonvulsive drugs/ or exp antiemetic drugs/ or exp antihistaminic drugs/ or exp antihypertensive drugs/ or exp benzodiazepines/ or exp cns depressant drugs/ or exp sedatives/ or exp antidepressant drugs/ or exp nonprescription drugs/ or exp self medication/ or exp prescription drugs/ or exp polypharmacy/
39		(insomnia or chronic pain or schizophrenia or major depression).id. and drug therapy.sh.
40		(zolpidem or zaleplon or eszopiclone or ambien or lunesta or sonata or benzodiazepine* or antidepressant* or anti-depressant* or stimulant* or 'z drug' or 'z drugs' or hypnotic* or psychoactive*).mp.
41		(over-the-counter or 'over the counter' or OTC).mp or (prescription* or prescribed).ab,ti. Or polypharmacy.mp.
42		((medication* or medicine) and (multiple or concomitant or several)).mp.
43	Combine	37 OR 38 OR 39 OR 40 OR 41 OR 42
44	Combine with chronic pain and LTOT	8 AND 43
45	Risk mitigation for addiction (KQ7)	exp opiates/ or exp drug addiction/ or exp prescription drugs/ or exp drug abuse/ or exp addiction/ OR (opiates.id and drug abuse.sh.)
46		((addict* OR abuse OR misuse OR diversion OR divert) AND (opi* OR oxymorphone OR tapentadol OR methadone OR fentanyl OR hydrocodone OR oxycodone OR codeine OR morphine OR hydromorphone OR tramadol)).mp.
47	Combine opiate addiction or misuse	45 OR 46
48	Mitigation strategies	urin* adj7 (screen* OR test* OR detect* OR anal* OR monitor*) OR exp urinalysis/ or exp drug usage screening/
49		Count OR 'call back' OR database OR query OR compliance OR contract* OR agreement OR consent OR recall OR surveillance OR call-back OR monitor* OR (‘pill count’ OR pill count).mp.
50		(naloxone adj2 rescue).mp.
51		'patient compliance'/exp OR (patient:ab,ti AND (compliance:ab,ti OR comply:ab,ti))
52		Exp treatment compliance/ or (patient and (compliance or comply)).ab,ti.
53		((office OR doctor OR primary) adj3 (visit* OR appointment* OR check*)).mp. OR (exp opiates/ AND exp monitoring/)
54		Exp client education/ or patient education.mp. OR patient NEXT/3 (aware* OR educat*)
55		(opi* adj5 (contract OR contracts OR agreement)).mp.
56	Combine mitigation strategies	48 OR 49 OR 50 OR 51 OR 52 OR 53 OR 54 OR 55

Set Number	Concept	Search Statement
57	Risk	Exp risk assessment/ or exp risk perception/ or (risk* adj7 (mitigate* OR reduc*)).mp. or (risk evaluation and mitigation strategy).mp.
58	Combine addiction, mitigation, and risk	47 AND 56 AND 57
59	Combine addiction, mitigation, and risk with LTOT	7 AND 58
60	Treatment of OUD (KQ8)	((addict* OR abuse OR misuse OR diversion OR divert) AND (opi* OR oxymorphone OR tapentadol OR methadone OR fentanyl OR hydrocodone OR oxycodone OR codeine OR morphine OR hydromorphone OR tramadol)).mp.
61	Opiate addiction or misuse	exp opiates/ or exp drug addiction/ or exp prescription drugs/ or exp drug abuse/ or exp addiction/ OR (opiates.id and drug abuse.sh.)
62		(exp drug abuse/ or exp drug dependence/ or exp drug addiction/ or aberrant.ti. or aberrant.ab.) and (exp opiates/ or opioid*.mp. or oxymorphone.mp. or tapentadol.mp. or methadone.mp. or fentanyl.mp. or hydrocodone.mp. or oxycodone.mp. or codeine.mp. or morphine.mp. or hydromorphone.mp. or tramadol.mp. or analgesic*.mp.)
63	Counseling	Exp psychotherapy/ OR exp cognitive therapy/ OR exp counseling/ OR exp support group/ OR exp motivational interviewing/ exp Adjunctive Treatment/ or exp Treatment Compliance/ or exp Treatment/ or exp Treatment Effectiveness Evaluation/ or (treat or treatment or therap* or counsel*s).ab,ti.
64		counsel OR counseling OR ((cognitive OR contingency OR drug OR behavioral OR motivational) adj2 (counseling OR therapy)) OR motivation* adj1 interview* OR (buprenorphine OR naloxone OR naltrexone OR methadone) OR contingency management.mp.
65	Combine addiction	60 OR 61 OR 62
66	Combine counseling	63 OR 64
67	Combine LTOT and addiction and counseling	7 AND 65 AND 66
68	Tapering (KQ9)	(exp analgesia/ or exp analgesic drugs/ or exp pain management/) AND exp drug dosages/
69		((dose or dosing) and (protocol* or administration or plan* or schedule* or strategy or strategies)).mp.
70		(taper* or decrease* or reduc* or adjust* or titrat* or dosing or dose*).mp.
71		((taper* or decrease* or reduc* or adjust* or titrat* or dosing or dose*) and (protocol* or administration or plan* or schedule* or strategy or strategies)).mp.
72	Combine tapering sets	68 OR 69 OR 70 OR 71
73	Combine tapering and chronic pain and LTOT	8 AND 72
74	Combine all final sets	15 OR 22 OR 30 OR 36 OR 44 OR 59 OR 67 OR 73
75	Apply limits	limit 74 to (human and english language and yr="2009 - 2016")
76	Apply publication type limits	75 AND (trial* or study or studies or method* or review* or analysis or compar* or random* or systematic*).mp.
77		limit 75 to ("0100 journal" or "0110 peer-reviewed journal" OR “journal article”)

Set Number	Concept	Search Statement
78		75 AND (exp clinical trials/ or exp cohort analysis/ or exp followup studies/ or exp longitudinal studies/ or ((compar* or comparison or comparative) and trial*).ab,ti.
79	Combine final sets	76 OR 77 OR 78

OVID syntax:

* (within or following a term) = truncation character (wildcard)

.ab. = limit to abstract

ADJn = search terms within a specified number (n) of words from each other in any order

exp/ = "explodes" controlled vocabulary term (e.g., expands search to all more specific related terms in the vocabulary's hierarchy)

.mp. = combined search fields (default if no fields are specified)

.pt. = publication type

.ti. = limit to title

.ti,ab. = limit to title and abstract fields

Table J-3. EMBASE/Medline Search Strategies Conducted using EMBASE Syntax

Set Number	Concept	Search Statement
1	Chronic pain	'chronic pain'/exp OR (chronic OR 'long term') NEXT/2 pain*
2		'chronic inflammatory pain'/de OR (chronic NEXT/3 pain*):ab,ti.
3	Combine sets for chronic pain	1 OR 2
4	LTOT	'narcotics'/exp OR 'narcotic agent'/exp OR 'analgesia'/exp OR 'narcotic analgesic agent'/exp OR 'opiate'/de
5		opioid* OR opiod* OR opiate* OR oposal OR opon OR narcotic*
6		'morphine'/de OR 'codeine'/de OR 'fentanyl'/de
7		Oxymorphone OR tapentadol OR methadone OR fentanyl OR hydrocodone OR oxycodone OR codeine OR morphine OR hydromorphone OR tramadol
8		'pain'/exp AND 'drug therapy'/lnk AND opi*
9	Combine sets for opioids	4 OR 5 OR 6 OR 7 OR 8
10	Combine with chronic	9 AND (chronic:ti OR 'cot':ti OR chronic NEXT/1 opi* NEXT/1 therapy OR longterm:ti OR 'long term':ti OR months:ab,ti OR year*:ab,ti)
11	Combine chronic pain with LTOT	3 AND 10
12	Contraindications (KQ1)	'drug contraindication'/exp OR 'drug interaction'/exp OR 'drug safety'/exp OR 'analgesics, opioid/contraindicaitons'

Set Number	Concept	Search Statement
13		Compensation* OR contraindication* OR copd OR cardiovascular OR respiratory OR 'chronic obstructive' OR lung OR fibromyalgia OR headache* OR heart OR liver OR sleep OR osteoporosis OR cns OR immune OR gastrointestinal OR medic* NEAR/1 marijuana OR 'post-traumatic stress' OR ptsd OR 'traumatic brain' OR tbi OR 'substance use disorder' OR sud OR depression OR suicide OR suicidality OR (personality OR cognitive OR mental OR neuro*) NEXT/3 (disorder* OR disease* OR illness*)
14	Combine contraindications	12 OR 13
15	Combine contraindications with chronic pain and LTOT	11 AND 14
16	Risk of misuse (KQ2)	('opiate addiction'/exp OR 'analgesic agent abuse'/exp OR 'opioid-related disorders'/exp) AND ('risk'/exp OR risk*:ab,ti)
17		'risk'/exp OR (risk* AND (predict* OR assess*))
18		(opi* OR narcotic* OR hydrocodone OR vicodin OR oxycodone OR oxycontin OR percocet OR heroin OR methadone OR morphine OR codeine OR analgesic*) NEXT/2 (addict* OR abuse OR misuse OR disorder OR diversion)
19	History of abuse	'domestic violence'/exp OR 'sexual abuse'/exp OR 'bullying'/exp OR bully OR bullying OR (domestic OR spous* OR child* AND (abuse OR violence))
20	Risk of opioid addiction	17 AND (18 OR 19)
21	Combine risk sets	16 OR 20
22	Combine risk of misuse with chronic pain and LTOT	11 AND 21
23	Effectiveness and Safety of LTOT (KQs 3 and 4)	'adverse drug events' OR 'ade' OR overdose OR diversion OR misuse OR addict* OR abuse OR adverse NEXT/1 event OR adverse NEXT/1 effect* OR accident* OR absence OR absent OR falls OR fall OR depression OR anxiety OR mood Or overdose* OR poison* OR death OR harm* OR disorder* OR sleep OR aberrant NEXT/3 behavior* OR complication* OR cardiovascular OR cardiac OR cognitive
24		'quality of life'/exp OR 'quality of life' OR qol OR pain NEXT/2 relief OR pain NEXT/2 reliev* OR ‘pain relief’
25		'prescription drugs'/exp AND ('adverse drug reaction'/lnk OR 'side effect'/lnk)
26		'treatment outcome'/de OR 'side effect'/de OR 'adverse drug reaction'/exp OR ‘drug overdose’/ OR ‘adverse outcome’/exp OR ‘opiate addiction’/exp OR 'patient safety'/exp OR safety OR effectiveness OR effective OR outcome*
27	Combine sets for safety	23 OR 24 OR 25 OR 26
28	Combine with chronic pain and LTOT	11 AND 27
29	Formulations (KQ5)	'narcotics'/exp OR 'narcotic agent'/exp OR 'analgesia'/exp OR 'narcotic analgesic agent'/exp OR 'opiate'/de
30		opioid* OR opiod* OR opiate* OR oposal OR opon OR narcotic* OR oxymorphone OR tapentadol OR methadone OR fentanyl OR hydrocodone OR oxycodone OR codeine OR morphine OR hydromorphone OR tramadol
31		'morphine'/de OR 'codeine'/de OR 'fentanyl'/de
32		'pain'/exp AND 'drug therapy'/lnk AND opi*

Set Number	Concept	Search Statement
33	Combine sets for opioids	29 OR 30 OR 31 OR 32
34		'immediate release' OR 'extended release' OR 'short acting' OR shortacting OR sa OR 'long acting' OR longacting OR la OR 'controlled release' OR (short* OR long* OR immediate OR extended OR controlled OR sustained AND (release* OR act*)) OR 'short acting analgesic agent'/exp OR (abuse-deterrant AND formula*)
35		33 AND 34
36		'opiate'/exp OR 'narcotics'/exp OR 'narcotic agent'/exp OR 'analgesia'/exp OR 'narcotic analgesic agent'/exp OR 'opiate'/de OR morphine OR oxycodone OR oxymorphone OR opi* AND (controlled OR sustained OR extended)
37	Opioid formulations	35 OR 36
38	Combine with chronic pain and LTOT	11 AND 37
39	Added benzodiazepines (KQ6)	'benzodiazepine derivative'/exp OR 'benzodiazepine' OR benzodiazepine* OR 'antidepressant agent'/exp OR 'hypnotic sedative agent'/exp OR 'narcotic analgesic agent'/exp OR 'benzodiazepine derivative'/exp OR 'zolpidem'/exp OR 'zaleplon'/exp OR 'eszopiclone'/exp
40		'zolpidem' OR 'zaleplon' OR 'eszopiclone' OR ambien OR lunesta OR sonata OR benzodiazepine* OR antidepressant* OR 'anti-depressant' OR 'anti depressant' OR stimulant* OR 'z drug' OR 'z drugs' OR hypnotic* OR psychoactive*
41		prescription* AND (otc OR 'over the counter') AND (multiple* OR added OR additional OR several OR concomitant)
42		'prescription drug'/exp AND 'non prescription drug'/exp OR 'polypharmacy'/exp
43	Combine medicine sets	38 OR 39 OR 40 OR 41
44		'treatment outcome'/de OR 'side effect'/de OR 'adverse drug reaction'/exp OR 'patient safety'/exp OR safety OR effectiveness OR effective OR outcome*
45	Combine with outcomes	42 AND 43
46	Combine with chronic pain and LTOT	11 AND 45
47	Risk mitigation for addiction (KQ7)	'opiate addiction'/exp OR 'substance abuse'/exp OR 'drug monitoring'/exp OR 'prescription drug diversion'/exp OR ((addict* OR abuse OR misuse OR diversion OR divert) AND (opi* OR oxymorphone OR tapentadol OR methadone OR fentanyl OR hydrocodone OR oxycodone OR codeine OR morphine OR hydromorphone OR tramadol))
48		urin* NEXT/7 (screen* OR test* OR detect* OR anal* OR monitor*) OR 'urinalysis'/exp
49		pill NEXT/2 count OR 'call back' OR database OR query OR compliance OR contract* OR agreement OR consent OR recall OR surveillance OR call-back OR monitor* OR naloxone NEXT/2 rescue
50		'patient compliance'/exp OR (patient:ab,ti AND (compliance:ab,ti OR comply:ab,ti))
51		'patient education'/exp OR patient NEXT/3 (aware* OR educat*)
52		(office OR doctor OR primary) NEXT/3 (visit* OR appointment* OR check*)
53		'contracts'/exp OR opi* NEXT/5 (contract OR contracts OR agreement)

Set Number	Concept	Search Statement
54		Risk* NEXT/7 (mitigate* OR reduc*) OR 'risk'/exp OR 'risk reduction'/exp OR 'risk evaluation and mitigation strategy' OR 'naloxone'/exp OR naloxone OR rescue OR precaution*
55	Combine risk mitigation strategies	47 OR 48 OR 49 OR 50 OR 51 OR 52 OR 53 OR 54
56	Combine with chronic pain and LTOT	11 AND 55
57	Treatment of OUD (KQ8)	addict* OR abuse OR misuse OR disorder AND (opi* OR oxymorphone OR tapentadol OR methadone OR fentanyl OR hydrocodone OR oxycodone OR codeine OR morphine OR hydromorphone OR tramadol) OR 'opiate use disorder'
58		'opiate addiction'/exp OR 'analgesic agent abuse'/exp OR ('drug abuse'/exp OR 'drug dependence'/exp OR 'narcotic dependence'/exp OR 'addiction'/exp OR aberrant:ti OR aberrant:ab AND ('narcotic analgesic agent'/exp OR 'opiates'/exp OR opioid* OR oxymorphone OR tapentadol OR methadone OR fentanyl OR hydrocodone OR oxycodone OR codeine OR morphine OR hydromorphone OR tramadol OR analgesic*))
59		'psychotherapy'/exp OR 'cognitive therapy'/exp OR 'counseling'/exp OR 'acceptance and commitment therapy'/exp OR 'support group'/exp OR 'motivational interviewing'/exp
60		counsel OR counseling OR (cognitive OR contingency OR drug OR behavioral OR motivational) NEAR/2 (counseling OR therapy) OR 'contingency management' OR motivation* NEAR/1 interview* OR buprenorphine OR naloxone OR methadone
61	Combine opioid addiction set	57 OR 58
62	Combine counsel set	59 OR 60
63	Combine with chronic pain and LTOT	11 AND 61 AND 62
64	Tapering (KQ9)	'pain management'/exp OR 'analgesia'/exp AND ('drug administration'/exp OR 'clinical protocol'/exp)
65		'dose response'/exp OR ((dose OR dosing) AND (protocol* OR administration OR plan* OR schedule* OR strategy OR strategies))
66		(taper* OR decrease* OR reduc* OR adjust* OR titrat* OR dosing OR dose*) AND (protocol* OR administration OR plan* OR schedule* OR strategy OR strategies)
67	Combine tapering sets	64 OR 65 OR 66
68	Combine with chronic pain and LTOT	11 AND 67
69	Combine all final sets	15 OR 22 OR 28 OR 38 OR 46 OR 56 OR 63 OR 68
70	Apply limits	69 AND [2009-2016]/py AND [English]/lim AND [humans]/lim
71	Apply unwanted publication types	70 NOT ('conference abstract'/it OR 'conference paper'/it OR 'editorial'/it OR 'letter'/it OR 'note'/it OR 'short survey'/it)
72	Apply trials hedge	71 AND (random*:ab,ti OR trial* OR control* OR cohort OR compar*:ab,ti OR prospective OR retrospective OR series OR review* OR study OR studies OR method* OR analysis OR systematic*:ab,ti)

Set Number	Concept	Search Statement
73		71 AND ('clinical trial'/exp OR 'clinical trial (topic)'/exp OR 'longitudinal study'/exp OR 'major clinical study'/exp OR 'prospective study'/exp OR 'retrospective study'/exp OR 'controlled clinical trial'/exp OR 'controlled clinical trial (topic)'/exp OR 'randomized controlled trial'/exp OR 'randomized controlled trial'/de OR 'comparative study'/exp OR 'methodology'/exp)
74		71 AND ('meta analysis'/de OR 'meta analysis (topic)'/exp OR 'meta analysis'/exp OR 'outcomes research'/exp OR 'systematic review'/exp OR 'systematic review (topic)'/exp OR 'systematic review'/de OR 'meta? analysis':ab,ti OR 'systematic review':ab,ti)
75	Combine	72 OR 73 OR 74

EMBASE.com Syntax:

* (within or following a term) = truncation character (wildcard)

:ab = limit to abstract

:ab,ti = limit to abstract and title

NEAR/n = search terms within a specified number (n) of words from each other in any order

/exp = "explodes" controlled vocabulary term (e.g., expands search to all more specific related terms in the vocabulary's hierarchy)

:it. = limit to publication type

:ti. = limit to title

Appendix K: Abbreviation List

Abbreviation	Definition
^{o}F	degrees Fahrenheit
AAAP	American Academy of Addiction Psychiatry
AAPM	American Academy of Pain Medicine
AHRQ	Agency for Healthcare Research and Quality
AIDS	acquired immunodeficiency syndrome
AMA	American Medical Association
AOR	adjusted odds ratio
APAP	acetaminophen
APTA	American Physical Therapy Association
ARR	adjusted risk ratio
ASA	acetylsalicylic acid
ASAM	American Society of Addiction Medicine
BID	two times per day
BPI	Brief Pain Inventory
CARF	Commission on Accreditation of Rehabilitation Facilities
CBT	Cognitive Behavioral Therapy
CDC	Centers for Disease Control and Prevention
CENTRAL	The Cochrane Central Register of Controlled Trials
CI	confidence interval
CNCP	chronic non-cancer pain
CNS	central nervous system
COI	conflict of interest
COPD	chronic obstructive pulmonary disease
COR	contracting officer's representative
CPG	clinical practice guideline
CS	clinical study
DATA 2000	Drug Addiction Treatment Act of 2000
DEA	Drug Enforcement Administration
dL	deciliter(s)
DoD	Department of Defense
DSM-IV	Diagnostic and Statistical Manual of Mental Disorders, Fourth Edition
DSM-5	Diagnostic and Statistical Manual of Mental Disorders, Fifth Edition
EBPWG	Evidence-Based Practice Work Group
ECG	electrocardiogram
EDDP	2-ethylidene-1,5-dimethyl-3,3-diphenylpyrrolidine
EMR	electronic medical record
FDA	Food and Drug Administration
FY	fiscal year
GCMS	gas chromatography- mass spectrometry

Abbreviation	Definition
GI	gastrointestinal
GRADE	Grading of Recommendations Assessment, Development and Evaluation
HHS	U.S. Department of Health and Human Services
HIV	human immunodeficiency virus
HR	hazard ratio
hr	hour
IOM	Institute of Medicine
IRR	incidence rate ratios
KQ	key question
LCMS	liquid chromatography-mass spectrometry
LOT	long-term opioid therapy
m	meter(s)
M3G	morphine-3-glucuronide
M6G	morphine-6-glucuronide
MAOI	monoamine oxidase inhibitor
MAT	medication assisted treatment
mcg	microgram(s)
MDA	3,4-methylenedioxy-amphetamine
MDEA	3,4-methylenedioxy-N-ethyl-amphetamine
MDMA	3,4-methylenedioxy-methamphetamine
MEDD	morphine equivalent daily dose
MeSH	Medical Subject Headings
mg	milligram(s)
MHS	Military Health System
mL	milliliter(s)
MRI	magnetic resonance imaging
NICE	National Institute for Health and Care Excellence
NSAIDs	non-steroidal anti-inflammatory drugs
OA	osteoarthritis
OEF	Operation Enduring Freedom
OEND	Opioid Overdose Education and Naloxone Distribution
OIF	Operation Iraqi Freedom
OR	odds ratio
OSI	Opioid Safety Initiative
OTC	over the counter
OTRR	Opioid Therapy Risk Report
OUD	opioid use disorder
PDMP	Prescription Drug Monitoring Program
PICOTS	population, intervention, comparison, outcome, timing, and setting
PPACA	Patient Protection and Affordable Care Act

Abbreviation	Definition
PRN	as needed
PTSD	posttraumatic stress disorder
QTc interval	the heart rate's corrected time interval from the start of the Q wave to the end of the T wave
RCT	randomized controlled trial
REMS	Risk Evaluation and Mitigation Strategy
SA	sustained action
SAMHSA	Substance Abuse and Mental Health Services Administration
SE	standard error
SL	sublingual
SMART	Specific, Measurable, Action Oriented, Realistic, Timed
SNRIs	serotonin-norepinephrine reuptake inhibitors
SR	sustained release
SSRI	selective serotonin reuptake inhibitor
STORM	Stratification Tool for Opioid Risk Mitigation
SUD	substance use disorders
THC	tetrahydrocannabinol
THCA	delta-9-tetrahydrocannabinol-9-carboxylic acid
TID	three times per day
U.S.	United States
UDT	urine drug testing (or urine drug test)
USPSTF	United States Preventive Services Task Force
UTS	urine toxicology screening
VA	Department of Veterans Affairs
VHA	Veterans Health Administration

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Chronic Opioid Therapy

Evidence Synthesis Report

Clinical Practice Guideline

Prepared for:

Veterans Health Administration, U.S. Department of Veterans Affairs,
and the U.S. Department of Defense

Submitted by:

ECRI Institute

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The LEWIN GROUP®

Center for Comparative Effectiveness Research

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Background and Purpose

ECRI Institute conducted a systematic review in support of the Department of Veterans Affairs and Department of Defense (VA/DoD) clinical practice guideline (CPG) on chronic opioid therapy (COT) for the management of chronic pain. This review assesses the benefits and harms associated with COT to manage chronic pain. The target audience of the systematic review and CPG are VA/DoD and non-VA/DOD primary care physicians who treat active and inactive military personnel.

The target population considered in this systematic review is adults (ages 18 years or older) with chronic cancer or non-cancer pain treated in any VA/DoD clinical setting. However, evidence from studies of patients with these conditions being managed outside the VA system will also be within the scope of the review.

Key Questions and Scope

This systematic review focused on evaluating the published evidence for the following 9 key questions (including sub-questions). These questions have been rated by the Champions and workgroup members as the priority questions to cover in this systematic review.

1. What is the evidence that the following medical or mental health conditions are absolute or relative contraindications of prescribing COT?
    - Active pursuit of compensation
    - Centralized pain conditions such as fibromyalgia
    - Chronic obstructive pulmonary disease
    - Cognitive impairment
    - Depression
    - Headache
    - Gastrointestinal (GI) motility problems (e.g., toxic megacolon, GI pain syndromes, narcotic bowel syndrome)
    - Immune status changes
    - Inability to participate in comprehensive treatment plan
    - Incarceration (history of)
    - Hepatic, renal, or pulmonary disease
    - Suspected opioid misuse (e.g., overdose, early refills, diversion, taking more than prescribed)
    - Osteoporosis
    - Personality disorders
    - Posttraumatic stress disorder
    - Sleep disorders
    - Substance use disorders (SUD) (current or history of)—include specific disorders and appropriate key words in search
    - Suicidality
    - Traumatic brain injury
    - Use of medical marijuana
    - QT prolongation

2. What factors increase the risk of developing misuse or opioid use disorder (OUD) when considering COT?
3. What is the comparative effectiveness of COT versus other treatment modalities?
    a. What is the comparative effectiveness of COT versus no opioid therapy or other treatment modalities for patients with a history of or current SUD?
4. What is the safety of COT versus other treatment modalities?
    a. What is the safety of COT versus other treatment modalities for patients with a history of or current SUD?
5. What is the comparative effectiveness and safety of various opioid formulations?
    a. Immediate-release/short-acting opioids compared to extended-release/long-acting opioids
    b. Route of administration/ delivery alternatives such as transdermal, buccal, sublingual, pumps
    c. Abuse deterrent formulations compared to non-abuse deterrent formulations
    d. Tramadol and other dual-mechanism opioids
    e. Buprenorphine
    f. Methadone
6. Does additional use of benzodiazepines or other psychoactive medications increase the risk of adverse events compared to opioid therapy alone?
7. What is the comparative effectiveness of different risk mitigation strategies for patients either on COT or being considered for COT?
    a. Does this differ for patients with history of or current SUD?
    b. Does this differ for patients with mental health comorbidities?
    c. Does this differ for patients with medical comorbidities?
8. What is the safety and effectiveness of treatment of OUD (diagnosed or suspected) in patients with chronic pain?
    a. Do outcomes vary by severity of OUD?
9. What is the safety and effectiveness of different tapering strategies and schedules?

Patients, Interventions, Comparators, Outcomes, Timing and Setting

Population(s): Adults 18 years or older with chronic cancer or non-cancer pain treated in any VA/DoD clinical setting.

Interventions: The table below lists the interventions that will be covered in this systematic review. The interventions are listed according to the key questions they address.

Table 1. Interventions

Key Question	Intervention(s)
1	Patients with a co-occurring medical or psychological condition on the following opioids: • Buprenorphine • Codeine • Hydrocodone • Hydromorphone

Key Question	Intervention(s)
	• Morphine • Oxycodone • Oxymorphone • Tapentadol • Tramadol • Fentanyl • Methadone
2	Opioid dosage Length of opioid use Other risk factors (**Examples** from Edlund et al. 2007;[1] **list may not be comprehensive**) • Age • Days with physical health care visits • Degree of pain • Gender • History of sexual abuse • History of abuse (including emotional, physical, or cyber bullying) or domestic violence • History of SUD—Self or familial • Marital status • Mental disorders • Non-opioid substance abuse • Race • Social status • Work status
3	See list of opioids under KQ1
4	See list of opioids under KQ1
5	Short-acting opioids • Codeine • Fentanyl • Hydrocodone (only in combination with acetaminophen and ibuprofen) • Hydromorphone • Morphine sulfate (tablet/liquid) • Oxycodone (alone or in combination with acetaminophen, ibuprofen, or aspirin) • Oxymorphone • Tramadol Long-acting/extended-release opioids • Buprenorphine transdermal system • Fentanyl transdermal system • Hydrocodone bitartrate extended-release capsules/tablets • Hydromorphone hydrochloride extended-release tablets • Methadone hydrochloride tablets • Morphine sulfate and naltrexone extended-release capsules • Morphine sulfate extended-release capsules/tablets • Oxycodone hydrochloride and naloxone hydrochloride extended-release tablets

Key Question	Intervention(s)
	• Oxycodone hydrochloride extended-release tablets • Oxymorphone hydrochloride extended-release tablets • Tapentadol extended-release oral tablets • Transdermal, buccal, sublingual, or pumps See main list of opioids. • Abuse deterrent formulations • Buprenorphine/Naloxone • Morphine/Naltrexone • OROS hydromorphone (Osmotic Extended-Release Oral delivery System) • Oxycodone Controlled Release • Oxymorphone • Additional medications • Tramadol and other dual-mechanism opioids • Buprenorphine • Methadone
6	Opioid therapy plus other psychoactive medications such as CNS depressants/antidepressants, non-opioid analgesics, benzodiazepines, stimulants, muscle relaxers, medical marijuana, Z-drugs (e.g., Zolpidem [Ambien], Eszopiclone [Lunesta], Zalepion [Sonata]), and over-the-counter sleep medications (e.g., diphenhydramine hydrochloride or doxylamine succinate)
7	Naloxone rescue with one form of naloxone Informed consent Use of written informed consent (previously called contracts) Risk assessment instruments Opioid management plans Patient education Urine drug testing (UDT) Prescription drug monitoring program (PDMP) Monitoring instruments More frequent monitoring Pill counts Use of abuse–deterrent formulations Diversion prevention interventions (e.g., properly securing drugs, medication take back programs, public health education) Pharmacogenetic testing Random call-backs Compliance with other therapies Case management Periodic check of state databases Needle exchange programs
8, 8a	Treatment with at least one of the following: • Buprenorphine (with or without naloxone) • Methadone • Injectable/oral naltrexone • Medical Management • Contingency Management

Key Question	Intervention(s)
	• Individual Drug Counseling • Motivational interviewing • Motivational Enhancement Therapy • Other motivational approaches
9	One tapering strategy or schedule

Comparator[s]: Table 2 lists the comparators of interest to this systematic review. The comparators are listed by the key question they address.

Table 2. Comparators

Key Question	Comparator(s)
1	Patients without a co-occurring medical or mental health condition on COT
2	Comparison groups that vary by COT dosage and length of opioid use, other factors
3	No opioid therapy (including placebo) or other pain management strategies Other modalities: • Non-opioid medications (e.g., non-steroidal including compounded topical preparations) • Physical interventions (e.g., physical therapy, active/passive exercise, ultrasound stimulation, chiropractic, osteopathic manipulation therapy) • Behavioral/mental health interventions EXAMPLES: ♦ Acceptance and commitment therapy (ACT) ♦ Cognitive behavioral therapy (CBT) ♦ Dialectical behavior therapy (DBT) ♦ Mindfulness • Complementary and alternative interventions EXAMPLES: • Acupuncture • Chiropractic interventions
4	No opioid therapy (including placebo) or other pain management strategies Other modalities: • Non-opioid medications (e.g., non-steroidal including compounded topical preparations) • Physical interventions (e.g., physical therapy, active/passive exercise, ultrasound stimulation, chiropractic, osteopathic manipulation therapy) • Behavioral/ mental health interventions (e.g., CBT, ACT, mindfulness, DBT) • Complementary and alternative interventions
5	Long-acting opioid drugs or combination short and long-acting drugs (See list) Other route of administration/delivery alternatives Non abuse-deterrent formulations Other opioids No use of buprenorphine No use of methadone
6	Opioid therapy alone
7	No mitigation strategy or other mitigation strategy
8	No treatment for OUD or other treatment for OUD

Key Question	Comparator(s)
9	Different tapering strategy or schedule

Outcomes(s): For the treatment and management questions (KQ 3–9), the following outcomes are of interest in the systematic review:

- Pain relief
- Quality of life
- Cognitive/functional status
- Mortality
- Opioid abuse/misuse
- Adverse events:
    - SUD
    - Aberrant use
    - Overdose
    - Non-pain use of opiates
    - Abuse
    - Addictions
    - Cardiovascular events
    - Respiratory depression
    - Gastrointestinal complications (including constipation)
    - Endocrinological complications (including impotence)
    - Weight gain
    - Cognitive performance
    - Psychiatric decompensation
    - Psychological symptoms (e.g., depression, loss of libido, nightmares)
    - Headaches
    - Suicide
    - Accidents (including falls)
    - Infections
    - Increased risk of HIV and Hepatitis A, B, and C
    - Loss to follow-up/medical care

Timing: 12 weeks for studies looking at the efficacy of opioid therapy; any follow-up for studies reporting on the safety of opioid therapy

Settings: Primary care

Methods of Systematic Review

The methods guiding this systematic review are described below. In part, these methods follow the guidelines for conducting a systematic review set forth by the Agency for Healthcare Research and Quality (AHRQ) in the "Methods Guide for Effectiveness and Comparative Effectiveness Reviews." Available: http://www.effectivehealthcare.ahrq.gov/index.cfm/search-for-guides-reviews-and-

reports/?productid=318&pageaction=displayproduct. The methods also follow the guidance set forth by the VA/DoD in the "Guidelines for Guidelines" document.

Study Selection Criteria

General Inclusion Criteria

- Clinical studies or systematic reviews published on or after March 1, 2009 to present. If multiple systematic reviews addressed a key question, we selected the most recent and/or comprehensive review. Systematic reviews will be supplemented with clinical studies published subsequent to the systematic review.
- Studies must be published in English.
- Publication must be a full clinical study or systematic review; abstracts alone were not included. Similarly, letters, editorials, and other publications that are not full-length clinical studies were not accepted as evidence.
- Study must have enrolled at least 20 patients (10 per study group) unless otherwise noted (see Key Question Specific Criteria below).
- Study must have reported on an outcome of interest. Study must have enrolled a patient population in which at least 80% of patients were receiving opioid therapy for chronic pain of at least 12 weeks' duration. If the percentage is less than 80%, then data must have been reported separately for this patient subgroup.
- For outcomes measuring treatment effectiveness, patients must have been followed for at least 12 weeks.
- For key question specific criteria, in the event that one or more KQs does not have sufficient evidence from the study designs specified below, lower-level evidence will be evaluated for that KQ (or KQs). Lower-level evidence was considered on a question-by-question basis, and inclusion of lower-level evidence is noted in individual key question chapters.

Key Question Specific Criteria

- For KQ 1, acceptable study designs included systematic reviews, randomized controlled trials (RCTs) or prospective cohort studies that statistically compared outcomes for patients with chronic pain and a co-occurring medical or mental health condition on COT to patients with chronic pain and no additional medical or mental health condition on COT. Large retrospective database studies (200 patients minimum) that performed multivariate statistical analyses of the effect of co-occurring conditions on patient outcomes were also acceptable.
- For KQ 2, acceptable study designs included systematic reviews, RCTs or prospective cohort studies that statistically compared outcomes for patients with chronic pain and differences in potential risk factors for developing opioid misuse or OUD. Large retrospective database studies (200 patients minimum) that performed multivariate statistical analyses of the effect of risk factors on patient outcomes are also acceptable.
- For KQs 3-6, 8, and 9, acceptable study designs included systematic reviews of RCTs and/or individual RCTs.
- For KQ 7, acceptable study designs included systematic reviews of RCTs, individual RCTs or prospective nonrandomized comparative studies.

Searching for the Evidence: Literature Search Strategies for Identifying Relevant Studies to Answer the Key Questions

Information professionals performing literature searches within the ECRI Institute Health Technology Assessment/EPC Information Center followed established guidelines and procedures as identified by the

Director of the Information Center. Consistent with our evidence-based searching protocol, for all key questions, we searched the following external and internal databases: MEDLINE, PreMEDLINE, EMBASE, and PsycINFO (via the OVID SP platform using the one-search and de-duplication features), the Cochrane Database of Systematic Reviews, the Database of Abstracts of Reviews of Effects, and the Health Technology Assessment Database. Searches were designed to identify unique reviews, trials, and technology assessments. Limited searches of the World Wide Web were also performed to capture relevant Limited searches of the Internet will be performed to capture relevant background information. Our searches covered the time period of March 1 2009 through January 18, 2016. Further details of our search strategy are provided in Appendix A.

We identified search terms by: (1) reviewing relevant systematic reviews on similar topics identified by members of the research staff; (2) reviewing how other relevant studies are indexed, their subject heading terms, and their keywords; (3) reviewing MeSH and EMTREE for relevant and appropriate terms, and (4) discussions with Champions. After reviewing these, we identified a combination of subject headings and keywords. Two team members and the medical librarian reviewed the search strategies developed using these terms. We applied a study-design filter to retrieve systematic reviews, comparative studies, and other study designs addressing the key questions of this review.

ECRI Institute staff members reviewed articles at the abstract level. We obtained for full review any articles possibly meeting the inclusion criteria for at least one of the key questions. Team members also reviewed all retrieved articles for inclusion; disagreements between them about full-length article inclusion were resolved by discussion and consensus.

Abstracting and Managing Data

For each study included in this review, we abstracted the following study level details: country, purpose, and quality rating. For previous systematic reviews, we reported the search strategy used, study selection criteria, and overall information about the evidence base, including number of included studies and overall patients enrolled. For all studies, we abstracted data about characteristics of the included patients and interventions being assessed.

Assessing Individual Studies' Methodological Quality (i.e., Internal Validity or Risk of Bias)

As per the VA/DoD Guidelines for Guidelines document, risk-of-bias (or study quality) of individual studies and previous systematic reviews was assessed using the U.S. Preventive Services Task Force (USPSTF) method. Each study was assigned a rating of Good, Fair, or Poor based on sets of criteria that vary depending on study design. Detailed lists of criteria and definitions of Good, Fair, or Poor ratings for different study designs appear in Appendix VII of the USPSTF procedure manual at http://www.uspreventiveservicestaskforce.org/Page/Name/methods-and-processes

Because the USPSTF does not have criteria specific for evaluation of prognostic studies, we rated the quality of prognostic studies using the recently-developed Quality in Prognosis Studies tool.[2] This instrument assesses potential bias related to six domains: study participation, study attrition, prognostic factor measurement, outcome measurement, study confounding, and statistical analysis and reporting.

Data Synthesis

We used a narrative approach to synthesizing the evidence for all the key questions. As indicated in the VA/DoD Guidelines for Guidelines document, the first line of evidence was previous systematic reviews. For questions in which a previous review was available, individual studies that met this review's inclusion criteria were used to supplement or update the previous review. We considered whether subsequent evidence supports the conclusions reported in the previous review. For questions for which no previous review was available, we summarized the overall findings for the outcomes of interest of the studies that addressed a key question.

Assessing the Overall Quality of the Body of Evidence for an Outcome

The overall quality of the body of evidence supporting the findings for the outcomes of interest in this report was assessed using the GRADE system. The GRADE system primarily involves consideration of the following factors: overall study quality (or overall risk of bias or study limitations), consistency of evidence, directness of evidence, and precision of evidence. Given time and resources, other factors such as publication bias may also be considered. The definitions of the factors listed above are provided in Table 3. For more information on the GRADE system go to the GRADE working group website at the following link: http://www.gradeworkinggroup.org/

The GRADE system rates the overall quality of the evidence as High, Moderate, Low, and Very Low. The overall quality of a body of evidence is rated based on the factors described in Table 3. For instance, a body of evidence that consists of RCTs automatically starts with a rating of high quality. This rating can be downgraded if some of the RCTs have serious flaws such as lack of blinding of outcome assessors, not reporting concealment of allocation, or high dropout rate. Similarly, the quality can be downgraded or further downgraded if inconsistencies of findings are present or if there is a lack of precision surrounding an outcome's effect size.

Table 3. GRADE Factors Used to Assess the Quality of a Body of Evidence

Evidence Category	Definition
Study Quality (Internal Validity or Risk of Bias)	Study quality takes into account the overall risk of bias rating of all the studies included in the evidence base. For the purpose of this review, the overall risk of bias would be the average or median USPSTF rating for studies comprising an evidence base for a key outcome.
Consistency of Evidence	Consistency of evidence refers to the degree of similarity in the direction of effects or the degree of similarity in the effect sizes (magnitude of effect) across individual studies within an evidence base.
Directness of Evidence	Direct evidence directly compares interventions of interest in populations of interest and measures patient-oriented outcomes. Evidence can be indirect if the tested intervention differs from the intervention of interest, the study population differs from the population of interest, the outcomes differ from those of primary interest, or treatment comparisons have not been tested in head-to-head comparisons.
Precision of Evidence	Precision is the degree of certainty surrounding an estimate of effect with respect to an outcome. Precision is primarily assessed by examining the 95% confidence intervals around the summary effect size.

Assessing Applicability

When describing the evidence base addressing a key question, we discussed aspects of the included studies, such as characteristics of included patients and treatments being assessed that may make the overall

findings of the studies more or less applicable to the population, treatments, or outcomes of interest to this review.

Results of Literature Searches

Extensive literature searches identified 8,474 citations potentially addressing the key questions of interest to this evidence review. Of those, 5,412 were excluded upon title review for clearly not meeting inclusion criteria (e.g., not pertinent to the topic, not published in English, published prior to study inclusion publication date, or not a full-length article). Overall, 3,062 abstracts were reviewed with 2,731 of those being excluded for the following reasons: not a systematic review or clinical study, did not address a key question of interest to this review, did not enroll a population of interest, or published prior to March 1 2009. A total of 331 full-length articles were reviewed. Of those, 130 were excluded at a first pass review for the following: not addressing a key question of interest, not enrolling the population of interest, not meeting inclusion criteria for clinical study or systematic review, not meeting inclusion criteria for any key question, or being a duplicate. A total of 201 full-length articles were thought to address one or more key questions and were further reviewed. Of these, 146 were ultimately excluded. Reasons for their exclusion are presented in Figure 1 below. A table listing all studies excluded at the full-article level is included as a separate file to this report.

Overall, 55 studies addressed one or more of the key questions and were considered as evidence in this review. Table 4 indicates the number of studies that addressed each of the questions. It should be noted that some papers addressed more than one key question. Therefore, the number of studies in Table 4 adds up to more than the total number of included studies.

Figure 1. Study Flow Diagram

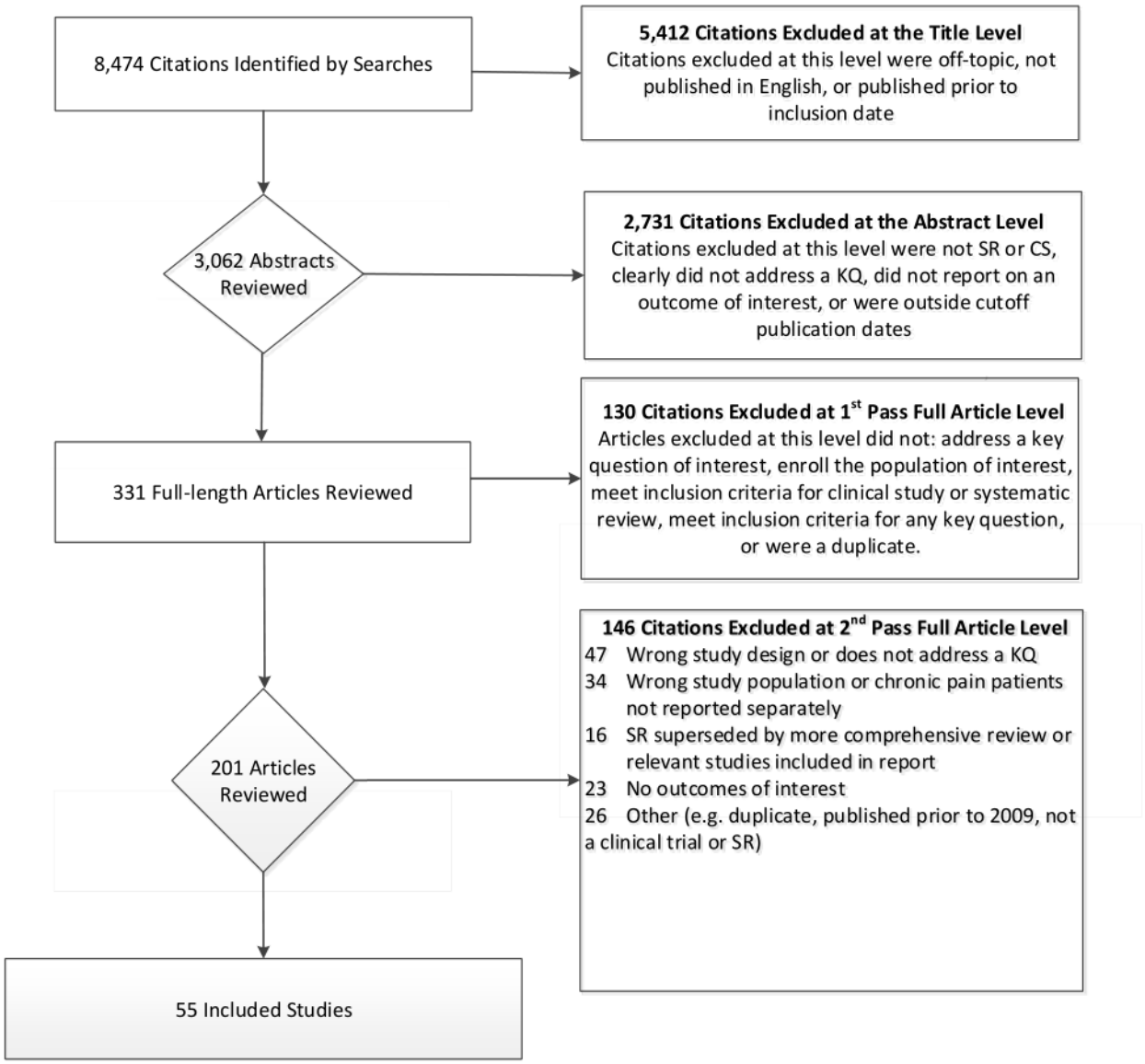
8,474 Citations Identified by Searches
5,412 Citations Excluded at the Title Level
Citations excluded at this level were off-topic, not published in English, or published prior to inclusion date
3,062 Abstracts Reviewed
2,731 Citations Excluded at the Abstract Level
Citations excluded at this level were not SR or CS, clearly did not address a KQ, did not report on an outcome of interest, or were outside cutoff publication dates
331 Full-length Articles Reviewed
130 Citations Excluded at 1st Pass Full Article Level
Articles excluded at this level did not: address a key question of interest, enroll the population of interest, meet inclusion criteria for clinical study or systematic review, meet inclusion criteria for any key question, or were a duplicate.
201 Articles Reviewed
146 Citations Excluded at 2nd Pass Full Article Level
47 Wrong study design or does not address a KQ
34 Wrong study population or chronic pain patients not reported separately
16 SR superseded by more comprehensive review or relevant studies included in report
23 No outcomes of interest
26 Other (e.g. duplicate, published prior to 2009, not a clinical trial or SR)
55 Included Studies

Table 4. Evidence Base for Key Questions

Number of Question	Question	Number of Studies and Type of Studies
1	What is the evidence that various medical or mental health conditions are absolute or relative contraindications of prescribing COT?	12 cohort studies 1 case-cohort study 1 nested case-control study
2	What factors increase the risk of developing misuse or OUD when considering COT?	10 cohort studies 1 case-cohort study 1 nested case-control study
3 and 4	What is the comparative effectiveness of COT versus other treatment modalities? a. What is the comparative effectiveness of COT versus no opioid therapy or other treatment modalities for patients with a history of or current SUD? And What is the safety of COT versus other treatment modalities? a. What is the safety of COT versus other treatment modalities for patients with a history of or current SUD?	1 systematic review and 17 RCTs
5	What is the comparative effectiveness and safety of various opioid formulations? a. Immediate-release/short-acting opioids compared to extended-release/long-acting opioids b. Route of administration/ delivery alternatives such as transdermal, buccal, sublingual, pumps c. Abuse deterrent formulations compared to non-abuse deterrent formulations d. Tramadol and other dual-mechanism opioids e. Buprenorphine f. Methadone	2 systematic reviews and 7 RCTs
6	Does additional use of benzodiazepines or other psychoactive medications increase the risk of adverse events compared to opioid therapy alone?	1 RCT 1 prospective comparison trial 1 post-hoc pooled analysis 1 retrospective cohort study
7	What is the comparative effectiveness of different risk mitigation strategies for patients either on COT or being considered for COT? a. Does this differ for patients with history of or current SUD? b. Does this differ for patients with mental health comorbidities? c. Does this differ for patients with medical comorbidities?	1 systematic review 1 prospective cohort study 1 retrospective database study
8	What is the safety and effectiveness of treatment of OUD (diagnosed or suspected) in patients with chronic pain? a. Do outcomes vary by severity of OUD?	1 systematic review and 2 RCTs
9	What is the safety and effectiveness of different tapering strategies and schedules?	1 RCT 1 prospective cohort study
Total Evidence Base (Note, some papers were used for more than one KQ)		**55 Studies**

Overview of Report

The remainder of the evidence report is divided into chapters, with each chapter addressing a key question. Each chapter describes the overall evidence base that addresses the question and provides details about the methodological quality of the included studies. Each chapter also describes the patients and treatments considered in the studies and includes a table summarizing the overall quality of the evidence (study profile tables). Finally, the chapters have their own appendices that include more detailed evidence tables, an excluded studies table, and reference list.

References

1. Edlund MJ, Steffick D, Hudson T, Harris KM, Sullivan M. Risk factors for clinically recognized opioid abuse and dependence among veterans using opioids for chronic non-cancer pain. Pain. 2007 Jun;129(3):355-62.
2. Hayden JA, van der Windt DA, Cartwright JL, Cote P, Bombardier C. Assessing bias in studies of prognostic factors. Ann Intern Med. 2013 Feb 19;158(4):280-6. Also available: http://dx.doi.org/10.7326/0003-4819-158-4-201302190-00009. PMID: 23420236

Key Question 1: What is the evidence that various medical or mental health conditions are absolute or relative contraindications of prescribing COT?

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Key Question 1: What is the evidence that various medical or mental health conditions are absolute or relative contraindications of prescribing COT?

Conditions to be considered for this key question include:

- Active pursuit of compensation
- Centralized pain conditions such as fibromyalgia
- Chronic obstructive pulmonary disease
- Cognitive impairment
- Depression
- Headache
- GI motility problems (e.g., toxic megacolon, GI pain syndromes, narcotic bowel syndrome)
- Immune status changes
- Inability to participate in comprehensive treatment plan
- Incarceration (history of)
- Hepatic, renal, or pulmonary disease
- Suspected opioid misuse (e.g., overdose, early refills, diversion, taking more than prescribed)
- Osteoporosis
- Personality disorders
- Posttraumatic stress disorder
- Sleep disorders
- SUD (current or history of)
- Suicidality
- Traumatic brain injury
- Use of medical marijuana
- QT prolongation

Summary of Evidence Base

Our literature searches identified 14 studies (mostly retrospective or prospective cohort studies) that provided potential evidence concerning contraindications to prescribing COT. None of the medical or mental health conditions associated with greater risk of negative patient outcomes can be considered absolute contraindications to COT (at least among the conditions for which there was an evidence base). However, conditions that increase the risk of negative outcomes could be considered relative contraindications to COT. This does not preclude prescribing COT in affected patients, but it does suggest that the potential benefits and harms of prescribing COT in these patients should be carefully weighed, and if COT is deemed appropriate, the patients should be carefully monitored for development of adverse

outcomes. The included studies evaluated the following medical or mental health conditions and their association with negative outcomes in chronic pain patients receiving opioid therapy.

- SUD or history of SUD
  - Pain: History of SUD did not have a significant effect on average daily pain improvement in patients treated with morphine or oxycodone for 6.5 months in one prospective cohort study (Quality of evidence: Low)
  - Opioid use disorder: History of SUD was significantly associated with opioid use disorder or opioid dependence in four cohort studies (Quality of evidence: Low to Moderate). Evidence supporting specific SUDs (e.g. alcohol use disorder) was conflicting or only represented by a single study, and two studies did not find evidence that smoking or illicit drugs were significantly associated with opioid dependence in multivariate analyses (Quality of evidence: Low).
  - Aberrant urine drug test (UDT) and non-adherence: One retrospective cohort study found that prior SUD diagnosis had a weak association with aberrant UDT results and non-detection of prescribed opioids in UDTs, but prior diagnosis of alcohol use disorder was not significantly associated with these results (Quality of evidence: Moderate).
  - Opioid-related respiratory/CNS depression or overdose: One case-control study reported that history of opioid dependence was significantly associated with opioid-related toxicity/overdose among veterans. Other substance abuse and non-opioid substance dependence had a weak association with the outcome (Quality of evidence: Low).
  - Overdose: A large retrospective cohort study found a significant relationship between alcohol or other drug abuse to drug overdose in a univariate analysis but not in the final adjusted multivariate model. The overall frequency of overdose was low (Quality of evidence: Moderate).
  - Overdose death: A large case-cohort study of VHA patients with opioid prescriptions found a significant association between SUD diagnosis and increased risk of opioid-related overdose death in both CNCP patients and cancer patients. The overall frequency of fatal overdose was low (Quality of evidence: Moderate).
  - Suicide attempts: A large retrospective cohort study that found drug use disorder and alcohol use disorder were significantly associated with suicide attempts for CSA and LA opioids (Quality of evidence: Moderate).
- Depression or history of depression
  - Pain, quality of life, function, sleep quality: A post hoc analysis of RCT data found that depression had no significant effect on pain severity, quality of life, function, or sleep quality (Quality of evidence: Very Low). It did find a small but significant negative impact on pain interference (Quality of evidence: Low).
  - Current opioid dependence: Two cross-sectional cohort studies reported conflicting results regarding depression and opioid dependence in multivariate analyses (one showed a significant relationship while the other did not) (Quality of evidence: Very Low).

- Lifetime opioid dependence: One cross-sectional cohort study found that history of major depression was significantly associated with lifetime opioid dependence in a univariate comparison but not in a multivariate model (Quality of evidence: Low).
- Opioid-related respiratory/CNS depression or overdose: One case-control study reported that history of depression was not significantly associated with opioid-related toxicity/overdose (Quality of evidence: Very Low).
- Overdose: One large retrospective cohort study found that the adjusted odds of overdose in a multivariate analysis were significantly higher for persons with depression than those without this diagnosis, regardless of opioid dose (Quality of evidence: Moderate).

- Mood disorders
  - Suicide attempts: One large retrospective cohort study found that mood disorders were significantly associated with suicide attempts for patients receiving CSA or LA opioids (Quality of evidence: Moderate).
- Borderline personality disorder (BPD)
  - Lifetime opioid dependence, suicide attempts, suicidal ideation: One cross-sectional cohort study found that BPD was significantly associated with all three of these outcomes (Quality of evidence: Low).
  - Other outcomes: The same study found that pain severity, pain interference, non-adherence, opioid medication problems, and lifetime accidental overdose were not significantly associated with BPD (Quality of evidence: Low).
  - Opioid-related respiratory/CNS depression or overdose: One case-control study reported that history of BPD had a small but significant association with opioid-related toxicity/overdose (Quality of evidence: Low).
- Antisocial personality disorder
  - Opioid dependence (current or lifetime): One cross-sectional cohort study reported that history of antisocial personality disorder was weakly associated with lifetime opioid dependence, but not current opioid dependence, in a multivariate model (Quality of evidence: Low).
- Generalized anxiety disorder or posttraumatic stress disorder (PTSD)
  - Opioid dependence: Two cross-sectional cohort studies reported that anxiety and PTSD were not significantly associated with pharmaceutical opioid dependence in multivariate analyses (Quality of evidence: Low).
  - Opioid-related respiratory/CNS depression or overdose: One case-control study reported that neither anxiety nor PTSD were significantly associated with opioid-related toxicity/overdose (Quality of evidence: Low).
  - Overdose: One large retrospective cohort study reported that anxiety or PTSD diagnosis was not significantly associated with drug overdose (Quality of evidence: Moderate).
  - Suicide attempts: One retrospective cohort study reported that prevalence of self-inflicted injuries was significantly higher among patients with PTSD (with or without other mental

health diagnoses) compared to patients with other mental health diagnoses or patients with no mental health diagnoses (Quality of evidence: Low).

- Wounds or violence-related injuries: One retrospective cohort study reported that wounds or violence-related injuries were not significantly associated with PTSD (Quality of evidence: Low).

- Psychotic disorder
  - Overdose: One large retrospective cohort study reported psychotic disorder was not significantly associated with drug overdose (Quality of evidence: Moderate).
- Negative affect
  - Pain improvement, opioid misuse, and adverse effects: One small prospective cohort study reported that patients with high negative affect had significantly lower pain improvement, greater opioid misuse, and more and intense opioid side effects compared to the low negative affect group (Quality of evidence: Low).
- Psychiatric disorders (excluding SUDs)
  - Aberrant UDT results and non-adherence: One retrospective cohort study found that mental health diagnosis was not significantly associated with aberrant UDT results or prescribed opioid non-detection in UDT (Quality of evidence: Moderate).
  - Overdose deaths: One large case-cohort study reported that a diagnosis of psychiatric disorders was significantly associated with increased risk of overdose death in CNCP patients but not in cancer patients (Quality of evidence: Moderate).
- Psychiatric disorders (excluding PTSD)
  - Opioid-related accidents and overdoses, alcohol and non-opioid related accidents and overdoses, and self-inflicted injuries: One retrospective cohort study found that for all three of these event categories, rates were significantly higher among opioid users with non-PTSD mental health disorders compared to opioid users with no mental health diagnoses (Quality of evidence: Low).
  - Wounds/injuries, violence-related injuries: The same study did not find a significant between-group difference in rates of these events (Quality of evidence: Low).
- Traumatic brain injury (TBI)
  - Suicide attempts: Im et al. found that TBI was weakly associated with suicide attempts for patients on CSA and LA opioids (Quality of evidence: Moderate).
- Charlson score/medical frailty
  - Opioid use disorder: One large retrospective study reported that Charlson score was not significantly associated with opioid use disorder in multiple regression models (Quality of evidence: Moderate).
  - Suicide attempts: One large retrospective cohort study found that medical frailty was not significantly associated with suicide attempts among patients receiving CSA and LA opioids (Quality of evidence: Moderate).

- Congestive heart failure diagnosis or use of QT-prolonging medications
  - Cardiac events: One retrospective cohort study found that congestive heart failure diagnosis and use of QT-prolonging medication was not significantly associated with development of cardiac events during 12 months' follow-up in patients taking methadone for pain relief (Quality of evidence: Moderate).
- Chronic obstructive pulmonary disease or sleep apnea
  - Opioid-related respiratory/CNS depression or overdose: One case-control study found that history of COPD was weakly associated with opioid-related toxicity/overdose. Sleep apnea also had a weak association with the outcome (Quality of evidence: Low).
  - Overdose deaths: One large case-cohort study reported that diagnosis of COPD, CVD or sleep apnea was weakly associated with reduced risk of overdose-related death for patients with CNCP. The effect did not reach statistical significance for patients with cancer (Quality of evidence: Moderate).
- Cognitive impairment
  - Opioid-related respiratory/CNS depression or overdose: One case-control study reported that history of dementia was not significantly associated with opioid-related toxicity/overdose (Quality of evidence: Low).
- Renal disease
  - Opioid-related respiratory/CNS depression or overdose: One case-control study reported that renal disease was weakly associated with opioid-related toxicity/overdose (Quality of evidence: Low).
- Liver disease
  - Opioid-related respiratory/CNS depression or overdose: One case-control study reported that mild liver disease was not significantly associated with opioid-related toxicity/overdose. The same was true for viral hepatitis (Quality of evidence: Low).
- Pancreatitis
  - Opioid-related respiratory/CNS depression or overdose: One case-control study reported that pancreatitis was significantly associated with opioid-related toxicity/overdose (Quality of evidence: Low).

Overview of Evidence Base

Our searches identified 14 individual studies that addressed this key question. These were primarily cohort studies (prospective[1] retrospective[2-8] or cross-sectional[9-11]) with the exceptions of one case-cohort study,[12] one nested case-control study,[13] and one post hoc analysis of RCT data.[14] Each study evaluated associations between potential risk factors (including medical or mental health conditions) and treatment outcomes in opioid-treated patients with chronic non-cancer pain (CNCP); the case-cohort study also separately evaluated patients with cancer-related pain. For this reason, they can be considered prognostic studies. The results of these studies can be used to assess whether any of these risk factors are absolute or relative

contraindications to chronic opioid therapy. Excluded studies and the reasons for exclusion appear in Table 3 (Appendix C).

Study Quality Rating

Because the USPSTF does not have criteria specific for evaluation of prognostic studies, we rated the quality of the majority of studies using the recently-developed Quality in Prognosis Studies tool.[15] The prospective and retrospective cohort studies were almost all rated as Fair quality using this instrument. The main limitation of these studies was that not all potential confounding variables were adjusted for in statistical analyses, which leaves doubt concerning the strength of any observed associations between a risk factor and a treatment outcome. One retrospective cohort study was rated as Poor quality because the statistical analysis of adverse events did not adjust for confounding variables and information on specific pain diagnoses was lacking.[8]

Cross-sectional cohort studies were rated as Poor quality because, in addition to having this same limitation, the measurement of all variables and outcomes at the same time point precluded assessment of causality (i.e. that a prognostic factor preceded outcome occurrence). Also, there were differences or potential differences between enrolled patients and those who were eligible but did not participate.

The post hoc RCT analysis was also rated as Poor quality due to numerous flaws, including high attrition, moderate participation by potential enrollees, statistical analysis did not control for important potential confounders, no information on how missing data was handled, and lack of statistical power to detect small differences between subgroups.[14]

The case-cohort study (Bohnert et al.[12]) and the nested case-control study (Nedler et al.[13]) were rated using USPSTF criteria for case-control studies. Bohnert et al. was rated as Fair quality because of slight limitations in use of medical records data and a small possibility of case misclassification. Nedler et al. was rated as Poor quality because the study did not report the percentage of patients with acute versus chronic pain or the percentage of patients receiving short-term opioid therapy versus COT.

For more detailed information, see quality rating descriptions in Table 2.

Overview of Study, Patient, and Intervention Characteristics

Below we summarize study, patient, and intervention characteristics for each of the included studies. Additional information can be found in Table 2.

Campbell et al. (2015) conducted two analyses of data from a cross-sectional cohort study. The first analysis included 1424 patients with CNCP who had received prescription opioids for more than six weeks (patients taking methadone or buprenorphine as opioid substitution therapy for heroin dependence were excluded). The median patient age was 58 years and 55% were female. The study used univariate and multivariate regression analyses to identify factors associated with past year pharmaceutical opioid dependence. These included (among others) various substance abuse diagnoses, aberrant behaviors, and mental health conditions.[10] The second analysis (published separately) included 978 patients from the same cohort who completed a module adapted from the International Personality Disorder Examination to screen for borderline personality disorder (BPD). Hierarchical regression models were conducted to examine whether BPD was independently associated with pain severity, interference, medication non-adherence, overdose, lifetime pharmaceutical opioid dependence, past 12-month suicidal thoughts and lifetime suicide

attempts after controlling for various sociodemographic and pain-related factors, other mental health disorders, and SUDs (alcohol and drug use disorders).[4]

Huffman et al. (2015) conducted a retrospective cohort study that included 199 patients who had undergone long-term opioid therapy for CNCP. The mean age was 46.5 years and 60.8% of patients were female. The study used logistic regression to determine whether history of non-opioid substance usage or OME dosage at time of admission increased the risk of therapeutic opioid addiction.[16]

Im et al. (2015) conducted a retrospective cohort study of 487,462 veterans who were prescribed chronic short-acting (CSA) or long-acting (LA) opioids from the VHA during fiscal year 2010. The mean age was not reported, but 93.5% of patients were male. The study used multivariate analyses to evaluate associations between guideline-recommended care, patient risk factors, and risk of suicide attempt. Potential patient risk factors evaluated in the analyses include drug/alcohol/mood disorders, traumatic brain injury, medical frailty and sociodemographic factors (age, gender and marital status). Patients were followed for 180 days following prescription initiation to document suicide attempts.[3]

Turner and Liang (2015) conducted a retrospective cohort study of 206,869 HMO patients with CNCP who received at least two Schedule II or III prescriptions for non-injectable opioid analgesics from January 2009 through July 2012. The mean patient age was 44.1 years (range 18 to 64 years) and 57% were female. The study used repeated measures logistic regression to evaluate interactions of filled prescriptions (including opioids, benzodiazepines, antidepressants, and zolpidem) with mental health disorders (anxiety/PTSD, depression, and psychotic disorder) in regard to drug overdose. Other factors included in the analyses were age, gender, region, SUD, clinical conditions, and opioid dose. Patients were followed for up to 3.5 years.[4]

Wasan et al. (2015) conducted a prospective cohort study of 81 patients who received morphine or oxycodone for chronic low back pain (CLBP). The study compared patients with high, moderate, and low negative affect to determine whether high negative affect is related to treatment failure. Negative affect was determined by the combined depression and anxiety subscale scores of the Hospital Anxiety and Depression Scale total score. The outcomes of interest included percent improvement in average daily pain during the opioid continuation period (primary outcome) as well as pain interference, opioid misuse, and opioid side effects. Linear mixed modeling was used to compare the low negative affect versus high negative affect groups over time. The mean patient age varied from 49 years (high negative affect group) to 55 years (low negative affect group); the percent of female patients ranged from 43% (moderate negative affect) to 67% (high negative affect). Only 55 patients completed the 6.5-month follow-up.[1]

Yarlas et al. (2015) performed a post hoc analysis of data from an RCT that enrolled 541 patients with CLBP who received either the buprenorphine transdermal system or placebo. The mean patient age was 49.5 years and 55% were female. The post hoc analysis used an analysis of covariance (ANCOVA) model to evaluate whether patients with depression have worse post-treatment outcomes than non-depressed patients. Outcomes of interest included pain severity, pain interference, quality of life, sleep quality, and functional disability. The follow-up period was 12 weeks.[14]

Edlund et al. (2014) conducted a retrospective cohort study of 568,640 patients with a new episode of a CNCP condition; the dataset was derived from a health plan database (HealthCore). All patients were at least 18 years old (mean age not reported) and 58% were female. The authors used logistic regression analysis to investigate the association between exposure to prescription opioids and incident opioid use disorders (OUDs). Other covariates in the adjusted analyses included opioid dose and days' supply, age in

years, gender, number of types of tracer pains in the pre-index period, number of non-tracer pain categories, number of non-substance mental health disorder types, pre-index substance abuse/dependence diagnoses, and Charlson score. The outcome of interest was any diagnosis of an OUD (opioid abuse or dependence) occurring in the 18-month period after the index date.[6]

Price et al. (2014) conducted a retrospective cohort study of 1,246 primary care patients prescribed methadone (chronic or non-chronic) for pain management. The mean patient age was 56 years and 61% were female. The authors performed multivariate logistical regression modeling to identify potential risk factors for cardiac adverse events (defined as either QTc prolongation ≥500 ms, hospitalization or ED visit without hospitalization for QTc prolongation/TdP, or cardiac death related to methadone use). Factors tested in the model included age, gender, chronic methadone use status, concomitant uses of QT-prolonging and CYP3A4-inhibiting medications, diagnosis of CHF, methadone dose at index date, dose ≥100 mg at any time during follow-up, and days of methadone supply during the 12-month follow-up.[7]

Turner et al. (2014) conducted a retrospective cohort study of 3,809 primary care patients on COT who underwent urinary drug testing (UDT). Patients were at least 20 years old (mean and range not reported) and 60.6% were female. Factors were evaluated in univariate logistic regression analyses to identify associations with aberrant UDT results. All predictors were entered in a multivariable model for each outcome that had sufficient counts for reliable results. Patient visit diagnoses were identified within 2 years prior to the index UDT.[5]

Zedler et al. (2014) conducted a retrospective nested case-control study of 8,987 veterans who received at least one opioid prescription from VHA during a two-year time period. The median patient age was 62 years and 92.1% were male. The "cases" were patients who had at least one opioid-related respiratory/CNS depression event or overdose during the study period. Each case was matched with 10 randomly selected controls who had received opioids during the same period but did not experience opioid-related toxicity or overdose. The authors used multivariable logistic regression to identify factors associated with a case event. The baseline period covered six months prior to the index event. For cases, the follow-up period was calculated as the number of days after the end of the event until death, disenrollment, or the end of the study period. Matched controls were given the same index-date and follow-up.[13]

Seal et al. (2012) performed a retrospective cohort study of 141,029 veterans with a non-cancer-related pain diagnosis; 15,676 received an opioid prescription for 20 or more consecutive days. The cohort was predominantly male (88.5%) and the mean age was not reported. The authors sought to assess the effect of mental health disorders (particularly PTSD) on risks and adverse clinical outcomes associated with prescription opioids. They determined the prevalence of adverse clinical outcomes for veterans within each mental health diagnostic category (no mental health diagnosis, mental health diagnosis without PTSD, and PTSD with or without another mental health diagnosis) who were and were not prescribed opioids for pain. The veterans were followed for one year from initial pain diagnosis to determine whether they received an opioid prescription and experienced an adverse clinical outcome.[8]

Bohnert et al. (2011) conducted a case-cohort study of 155,434 veterans treated with prescription opioids for CNCP, cancer, acute pain, and SUD. Only the first two groups were within the scope of our review, and the authors performed separate analyses for each patient subgroup. All patients were at least 18 years old (mean age was not reported) and 93.3% were male. The authors used Cox proportional hazards models to evaluate the association of opioid dose and dosing schedule with risk of opioid overdose death. Other

factors included in the models were pain-related diagnoses, other diagnoses (SUD; psychiatric disorders; COPD, CVD, and sleep apnea), gender, age, and race. The mean length of follow-up was not reported.[12]

Boscarino et al. (2010) performed a cross-sectional cohort study of 705 patients who received at least four opioid prescriptions for non-cancer pain over a one-year period. Mean patient age and gender were not reported. Patients underwent structured diagnostic interviews that included a modified Composite International Diagnostic Interview (CIDI); substance misuse and dependence were defined using DSM-IV criteria collected by the CIDI instrument. The authors used univariate and multivariate logistic regression to identify risk factors for opioid dependence. Variables assessed as potential risk factors included age, gender, current psychotropic drug use, various mental health conditions, and history of substance use/dependence (opioids, alcohol, illicit drugs, and smoking were separate variables). Outcomes were measured at time of interview, while some risk factor data came from medical records covering the past 3 years prior to the interview.[11]

Outcomes and Synthesis of Results

Below we summarize the outcomes and results of the evidence base that addressed this key question. For additional information on study results see Tables 1–3. Note that in observational studies, many epidemiologists consider odds ratios (ORs) and relative risks (RR) of less than 3, and especially less than 2, are considered weak or very weak associations that could be explained by confounding or even chance.

Substance Use Disorders or History of Substance Use Disorders

Average daily pain: The prospective cohort study by Wasan et al. reported that history of SUD did not have a significant effect on average daily pain improvement in patients treated with morphine or oxycodone for 6.5 months.[1]

OUD, therapeutic opioid addiction, opioid dependence: Edlund et al. conducted a large retrospective cohort study that found a significant association between pre-index alcohol use disorder (odds ratio [OR] 3.2) and non-opioid drug abuse disorders (OR 8.3) and post-index (18 months follow-up) OUD.[6] In a smaller retrospective cohort study, Huffman et al. found that lifetime history of SUD was strongly associated with therapeutic opioid addiction (OR=28.5). In a cross-sectional cohort study, Campbell et al. found that patients with past year pharmaceutical opioid dependence were significantly more likely to engage in aberrant behaviors (RR 2.47) and to meet criteria for lifetime benzodiazepine dependence (RR 3.22). However, other SUDs (smoking, alcohol, illicit drugs) were not significantly associated with pharmaceutical opioid dependence.[10] Similarly, Boscarino et al. found that history of opioid abuse and severity of opioid dependence were significantly associated with current and lifetime opioid dependence in multivariate models, while other SUDs (smoking, alcohol, illicit drugs) were not significantly associated with opioid dependence in these models.[11] These latter two studies differed from the first two in measuring all variables at the same time point, which precludes ascertainment of causality, and they were overall more susceptible to bias.

Aberrant results (from urine drug tests [UDT]): Turner et al. found that prior SUD diagnosis had a weak association with aberrant UDT results (OR 1.42, 95% CI: 1.17 to 1.72), but prior diagnosis of alcohol use disorder was not significantly associated with aberrant UDT results.[5]

Non-adherence: Turner et al. also found that prior SUD diagnosis had a weak association with non-detection of prescribed opioids in UDT results (OR 1.70, 95% CI: 1.31 to 2.20). The study did not find a significant association between alcohol use disorder and non-adherence as measured by UDT.[5]

Opioid-related respiratory/CNS depression or overdose: Zedler et al. reported that history of opioid dependence was significantly associated with opioid-related toxicity/overdose (OR 3.9, 95% CI: 2.6 to 5.8). Other substance abuse and non-opioid substance dependence had a weak association with the outcome (OR 1.4, 95% CI: 1.0 to 1.8).[13]

Overdose: Turner and Liang conducted a large retrospective cohort study among patients who filled two or more opioid prescriptions for CNCP that reported a significant relationship between alcohol or other drug abuse to drug overdose in a univariate analysis, but not in the final adjusted multivariate model. The overall frequency of overdose was low (0.67%).[4]

Overdose death: Bohnert et al. performed a large case-cohort study of VHA patients with opioid prescriptions that found a significant association between SUD diagnosis and increased risk of opioid-related overdose death in both CNCP patients (HR 2.53, 95% CI: 1.99 to 3.22) and cancer patients (HR 3.08, 95% CI: 1.73 to 5.51). However, the overall frequency of fatal overdose was low (estimated at 0.04%).[12]

Suicide attempts: Im et al. conducted a large retrospective cohort study that found drug use disorder and alcohol use disorder were significantly associated with suicide attempts for CSA and LA opioids. The rates of attempted suicide for patients with SUD were 7.2% (CSA opioids) and 8.3% (CSA opioids).[3]

Depression or History of Depression

Pain severity: Yarlas et al. performed a post hoc analysis of data from a large RCT of patients receiving BTDS or placebo for chronic low back pain. They found that depression had no significant effect on pain severity (Cohen's d=0.13, p>0.05).[14]

Pain interference: Yarlas et al. found that depression had a small but significant negative impact on pain interference (Cohen's d=0.29, p<0.01).[14]

Quality of life: Yarlas et al. found that depression had no significant effect on health-related QOL (Cohen's d ranged from 0.06 to 0.17 for various domains).[14]

Function: Yarlas et al. reported that depression had no significant effect on function (Cohen's d=0.08, p>0.05).[14]

Sleep quality: Yarlas et al. reported that depression had no significant effect on sleep quality (Cohen's d ranged from 0.01 to 0.13 for various domains).[14]

Current opioid dependence: Two cross-sectional cohort studies reported conflicting results regarding depression and opioid dependence in multivariate analyses. Campbell et al. did not find a significant association between depression and pharmaceutical dependence,[10] while Boscarino et al. found a very weak association (OR 1.29, p=0.022).[11] These studies had very serious limitations due to the cross-sectional analyses that preclude ascertainment of causality.

Lifetime opioid dependence: Boscarino et al found that history of major depression was significantly associated with lifetime opioid dependence in a univariate comparison but not in a multivariate model.[11]

Opioid-related respiratory/CNS depression or overdose: Zedler et al. reported that history of depression was not significantly associated with opioid-related toxicity/overdose (OR 1.2, 95% CI: 1.0 to 1.5, p=0.105).[13]

Overdose: Turner and Liang's multivariate analysis found an interaction between opioid therapy and depression, and that the adjusted odds of overdose were significantly higher for persons with depression than those without this diagnosis, regardless of opioid dose (all p<0.001).[4]

Mood Disorders

Suicide attempts: Im et al. found that mood disorders were significantly associated with suicide attempts for CSA and LA opioids (OR 3.5 and 3.9, respectively).[3]

Borderline Personality Disorder

Lifetime opioid dependence: Campbell et al. conducted a multivariate analysis that found a significant independent association between BPD and lifetime opioid dependence OR 2.49, 95% CI: 1.42 to 4.38).[9]

Suicidal ideation (past 12 months): Campbell also found that patients with BPD had 2.9 times the odds of experiencing past 12-month suicidal ideation (p<0.001).[9]

Lifetime suicide attempts: Campbell reported that patients with BPD had 3.2 times the odds of experiencing a lifetime suicide attempt (p<0.001).[9]

Other outcomes: In their hierarchical regression analyses, Campbell et al. found that pain severity, pain interference, non-adherence, opioid medication problems, and lifetime accidental overdose were not significantly associated with BPD.[9]

Opioid-related respiratory/CNS depression or overdose: Zedler et al. reported that history of BPD had a weak association with opioid-related toxicity/overdose (OR 1.7, 95% CI: 1.2 to 2.4).[13]

Antisocial Personality Disorder

Opioid dependence (current or lifetime): Boscarino et al. reported that history of antisocial personality disorder was weakly associated with lifetime opioid dependence in a multivariate model (OR=1.44, p=0.015). It was not associated with current opioid dependence in a multivariate model.[11]

Generalized Anxiety Disorder or Posttraumatic Stress Disorder

Opioid dependence: Campbell et al. and Boscarino et al. reported that anxiety and PTSD were not significantly associated with pharmaceutical opioid dependence in multivariate analyses (Boscarino had found an association in univariate analyses but not in the final multivariate analyses).[10,11]

Opioid-related respiratory/CNS depression or overdose: Zedler et al. reported that Neither anxiety nor PTSD were significantly associated with opioid-related toxicity/overdose (OR 1.1 and 1.0, respectively).

Overdose: Turner and Liang reported that anxiety or PTSD diagnosis was not significantly associated with drug overdose.[4] Seal et al. reported that opioid-related overdose was not significantly higher among patients with PTSD (with or without other mental health diagnoses) compared to patients with other mental health diagnoses, but was significantly higher compared to patients with no mental health diagnosis. They also

reported that PTSD (with or without other mental health diagnoses) was significantly associated with increased risk of alcohol and non-opioid drug-related overdose.[8]

Suicide attempts: Seal et al. reported that prevalence of self-inflicted injuries was significantly higher among patients with PTSD (with or without other mental health diagnoses) compared to patients with other mental health diagnoses or patients with no mental health diagnoses.[8]

Wounds or violence-related injuries: Seal et al. reported that wounds or violence-related injuries were not significantly associated with PTSD.[8]

Psychotic Disorder

Overdose: Turner and Liang reported that psychotic disorder was not significantly associated with drug overdose.[4]

Negative Affect

Average daily pain improvement: In their comparison of high and low negative affect subgroups among patients with CLBP, Wasan et al. found that the high negative affect group had a significantly smaller average improvement in pain than the low negative affect group (21% vs. 39%, $p<0.01$) at the end of follow-up (6.5 months). This difference occurred despite a higher average prescribed daily opioid dose in the high negative affect group (94.7 mg/day) compared to the low negative affect group (75.6 mg/day).[1]

Opioid misuse: Wasan et al. reported that the high negative affect group had a significantly greater rate of opioid misuse than the low negative affect group (39% vs. 8%, $p=0.013$).[1]

Adverse effects: Wasan et al. also found that the high negative affect group had significantly more and intense opioid side effects than the low negative affect group ($p=0.0001$).[1]

Psychiatric Disorders (Excluding Substance Use Disorders)

Aberrant results (from urine drug tests [UDT]): Turner et al. found that mental health diagnosis was not significantly associated with aberrant UDT results (OR 1.11, 95% CI: 0.96 to 1.27).[5]

Non-adherence: Turner et al. also found that mental health diagnosis was not significantly associated with prescribed opioid non-detection in UDT (OR 1.19, 95% CI: 0.99 to 1.44).[5]

Overdose deaths: Bohnert et al. found that a diagnosis of psychiatric disorders was weakly associated with increased risk of overdose death in CNCP patients (HR 1.87, 95% CI: 1.48 to 2.38) but not in cancer patients (HR 1.68, 95% CI: 0.95 to 3.00).[12]

Psychiatric Disorders (excluding PTSD)

Opioid-related accidents and overdoses, alcohol and non-opioid related accidents and overdoses, and self-inflicted injuries: Seal et al. found that for all three of these event categories, rates were significantly higher among opioid users with non-PTSD mental health disorders compared to opioid users with no mental health diagnoses ($p<0.001$).[8]

Wounds/injuries, violence-related injuries: Seal et al. did not find a significant between-group difference in rates of these events.[8]

Traumatic Brain Injury

Suicide attempts: Im et al. found that TBI was weakly associated with suicide attempts for patients on CSA and LA opioids (OR 1.31 and 1.5, respectively).[3]

Charlson Score/Medical Frailty

Opioid use disorder (abuse or dependence): Edlund et al. reported that Charlson score was not significantly associated with opioid use disorder in multiple regression models.[6]

Suicide attempts: In multivariate regression analyses, Im et al. found that medical frailty was not significantly associated with suicide attempts among patients receiving CSA and LA opioids.[3]

Congestive Heart Failure Diagnosis or Use of QT-Prolonging Medications

Cardiac events: Price et al. found that congestive heart failure diagnosis and use of QT-prolonging medication was not significantly associated with development of cardiac events during 12 months follow-up in patients taking methadone for pain relief.[7]

Chronic Obstructive Pulmonary Disease or Sleep Apnea

Opioid-related respiratory/CNS depression or overdose: Zedler et al. reported that history of COPD was weakly associated with opioid-related toxicity/overdose (OR 1.5, 95% CI: 1.2 to 1.9). Sleep apnea also had a weak association with the outcome (OR 1.3, 95% CI: 1.0 to 1.8).[13]

Overdose deaths: In multivariate regression models, Bohnert et al. found that diagnosis of COPD, CVD or sleep apnea was weakly associated with reduced risk of overdose-related death for patients with CNCP (HR 0.63, 95% CI: 0.50 to 0.80). The effect did not reach statistical significance for patients with cancer (HR 0.73, 95% CI: 0.38 to 1.42).[12]

Cognitive Impairment

Opioid-related respiratory/CNS depression or overdose: Zedler et al. reported that history of dementia was not significantly associated with opioid-related toxicity/overdose (OR 1.0, 95% CI: 0.3 to 3.1).[13]

Renal Disease

Opioid-related respiratory/CNS depression or overdose: Zedler et al. found that renal disease was weakly associated with opioid-related toxicity/overdose (OR 1.7, 95% CI: 1.3 to 2.4).[13]

Liver Disease

Opioid-related respiratory/CNS depression or overdose: Zedler et al. reported that mild liver disease was not significantly associated with opioid-related toxicity/overdose (OR 1.6, 95% CI: 0.9 to 3.2). The same was true for viral hepatitis (OR 1.4, 95% CI: 0.9 to 2.0).[13]

Pancreatitis

Opioid-related respiratory/CNS depression or overdose: Zedler et al. reported that pancreatitis was significantly associated with opioid-related toxicity/overdose (OR 2.2, 95% CI: 1.1 to 4.5).[13]

Overall Quality of Evidence Rating

The overall quality of the evidence was assessed for each outcome using the GRADE system, which assigns a rating of High, Moderate, Low or Very low. By default, RCTs start at High quality of evidence and observational intervention studies start at Low quality of evidence. The evidence is then assessed for potential deficiencies in four primary domains: overall study quality (usually the average or median quality of individual studies for each outcome), indirectness (of interventions, study populations, outcomes, and/or comparisons), inconsistency (in direction and/or magnitude of effect) and imprecision (uncertainty in the estimate of effect due to variance or low sample size). Deficiencies in any of these domains may result in downgrading the quality of evidence by one or two levels. Table 1 below presents the overall quality ratings for the predictors/outcomes assessed in each prognostic study.

Substance Use Disorders or History of Substance Use Disorders

The overall quality of evidence for the association of SUDs with negative outcomes in opioid-treated patients with CNCP covered a range from Low (pain improvement, opioid dependence) to Moderate (opioid use disorder, therapeutic opioid addiction, overdose, suicide attempts, opioid-related overdose deaths). Pain improvement and overdose were the only outcomes that did not show a significant negative association with current SUD diagnosis or history of SUDs. However, one study that combined overdose with opioid-related respiratory depression did find a significant association with history of SUDs. A Low grade resulted from very serious study limitations or a combination of serious study limitations and serious imprecision (if the only evidence was from one small study). A Moderate rating resulted only from serious study limitations.

Depression or History of Depression

The quality of evidence for depression and negative outcomes varied from Very Low (pain severity, quality of life, function, sleep quality, and current opioid dependence) to Low (pain interference, lifetime opioid dependence) to Moderate (overdose). Pain interference and overdose were the only outcomes with a clear significant negative association with depression (opioid dependence had somewhat mixed findings). Very Low grades resulted from a combination of very serious limitations and serious imprecision or inconsistency, while Low grades stemmed solely from very serious limitations. The only Moderate rating was for a study that had serious limitations but no deficiencies in other quality domains.

Mood Disorders

The quality of evidence from the single study that evaluated mood disorders was Moderate due to serious limitations; the study found a significant association with suicide attempts in patients on CSA or LA opioids.

Borderline Personality Disorder

The quality of evidence from the two studies that evaluated BPD was Low for all outcomes due to very serious study limitations. One study found a significant association between BPD and lifetime opioid dependence, suicidal ideation, and lifetime suicide attempts, but no significant relationship between BPD and pain-related outcomes, non-adherence, and lifetime accidental overdose. The other study found a small but significant association between BPD and opioid-related toxicity or overdose.

Antisocial Personality Disorder

The quality of evidence supporting a significant association between antisocial personality disorder and lifetime opioid dependence (but not current opioid dependence) was Low because of very serious limitations in the sole relevant study.

Generalized Anxiety Disorder or Posttraumatic Stress Disorder

The quality of evidence ranged from Low to Moderate for different outcomes. Two cross-sectional studies with very serious limitations provided Low-quality evidence that anxiety and PTSD were not associated with opioid dependence in multivariate analyses. One large retrospective cohort study with serious limitations provided Moderate-quality evidence that anxiety or PTSD were not significantly associated with drug overdose (this was also confirmed by a Low-quality case-control study at least with respect to opioid-related overdose). A Low-quality study (with very serious limitations) provided evidence that PTSD with or without other mental disorders was associated with increased risk of alcohol or non-opioid drug-related accident/overdose and self-inflicted injuries.

Psychotic Disorder

The quality of evidence was Moderate based on a single large retrospective cohort study with serious limitations that found psychotic disorder was not significantly associated with drug overdose.

Negative Affect

The quality of evidence was Low based on a single small prospective cohort study with serious limitations and imprecision that found a negative association between high negative affect and average pain improvement, opioid misuse, and adverse effects.

Psychiatric Disorders (Excluding Substance Use Disorders)

The quality of evidence was Moderate based on one large case-cohort study and one retrospective cohort study with serious limitations that found a significant association between diagnosed psychiatric disorders and aberrant UDT results and an increased risk of overdose death in CNCP patients.

Psychiatric Disorders (Excluding PTSD)

The quality of evidence was Low based on one case-control study with very serious limitations that found significantly higher rates of opioid-related accidents and overdoses, alcohol and non-opioid related accidents and overdoses, and self-inflicted injuries among opioid users with non-PTSD mental health disorders compared to patients with no mental health diagnoses.

Traumatic Brain Injury

The quality of evidence was Moderate based on one retrospective cohort study with serious limitations that found a significant association between TBI and increased risk of suicide attempts for patients on CSA and LA opioids.

Charlson Score/Medical Frailty

The quality of evidence was Moderate based on two large retrospective cohort studies with serious limitations. One study found no significant association between Charlson score and opioid use disorder while the other found no association between medical frailty and suicide attempts.

Congestive Heart Failure Diagnosis or Use of QT-Prolonging Medications

The overall quality of evidence was Moderate based on one retrospective cohort study with serious limitations that found CHF diagnosis and use of QT-prolonging medication was not significantly associated with development of cardiac events during 12 months follow-up in patients taking methadone for pain relief.

Chronic Obstructive Pulmonary Disease or Sleep Apnea

The overall quality of evidence was Low to Moderate based on case-control studies. One study with very serious limitations found Low-quality evidence of significant associations for both COPD and sleep apnea with opioid-related toxicity or overdose (the effect size was small for sleep apnea). In contrast, one study with serious limitations found that diagnosis of COPD, CVD or sleep apnea was associated with significantly reduced risk of overdose-related death for patients with CNCP.

Cognitive Impairment

The quality of evidence was Very Low based on a single case-control study with very serious limitations and serious imprecision in the effect estimate; it found no significant association between history of dementia and opioid-related toxicity/overdose.

Renal Disease

The quality of evidence was Very Low based on a single case-control study with very serious limitations that found a significant association between renal disease and opioid-related toxicity/overdose.

Liver Disease

The quality of evidence was Very Low based on a single case-control study with very serious limitations and serious imprecision in the effect estimates; it found no significant association between either mild liver disease or viral hepatitis and opioid-related toxicity/overdose.

Pancreatitis

The quality of evidence was Very Low based on a single case-control study with very serious limitations that found a significant association between renal disease and opioid-related toxicity/overdose.

Table 1. Overall Assessment of Quality of Evidence Base

Outcome	Quantity and Type of Evidence	Intervention (Number of Patients)	Findings	Study Limitations (Study Quality, Risk-of-Bias)[a]	Inconsistency[b]	Indirectness[c]	Imprecision[d]	GRADE of Evidence for Outcome
SUD or History of SUD								
Average daily pain	1 prospective cohort study (Wasan et al. 2015)[1]	Morphone or oxycodone (55 patients); mean MED 75.6 to 94.7 mg/day	History of SUD did not have a significant effect on average daily pain improvement after 6.5 months (F 0.78, p=0.38)	Serious limitations (-1)	No serious inconsistency	No serious indirectness	Serious imprecision (-1) (1 small study)	Low
Opioid use disorder (abuse or dependence)	1 retrospective cohort study (Edlund et al. 2014)[6]	Short-acting and/or long-acting opioids (568,640 patients); MED range 0 to >120 mg/day	Individuals with a pre-index alcohol use disorder had a higher likelihood of a post-index OUD (adjusted OR 3.22, 95% CI: 1.79, 5.80, p<0.001) compared to those with no pre-index alcohol use disorder. Similarly, those with pre-index non-opioid drug abuse disorders had higher rates of OUDs (OR=8.26, 95% CI: 4.74, 14.39, p<0.001) than those without pre-index non-opioid drug abuse disorders.	Serious limitations (-1)	No serious inconsistency	No serious indirectness	No serious imprecision	Moderate
Therapeutic opioid addiction	1 retrospective cohort study (Huffman et al. 2015[2]	Prescription opioids (199 patients); mean MED 132.85 (SD 175.39) mg/day	The presence of a lifetime history of an SUD was associated with 28 times increased odds of TOA (OR 28.5; 95% CI: 10.86 to 75.27).	Serious limitations (-1)	No serious inconsistency	No serious indirectness	No serious imprecision	Moderate

Outcome	Quantity and Type of Evidence	Intervention (Number of Patients)	Findings	Study Limitations (Study Quality, Risk-of-Bias)[a]	Inconsistency[b]	Indirectness[c]	Imprecision[d]	GRADE of Evidence for Outcome
Opioid dependence (current or lifetime)	2 cross-sectional cohort studies (Campbell et al. 2015;[10] Boscarino et al. 2010)[11])	Prescription opioids: Campbell (1,424 patients); median MED 75 (95% CI: 36–145) mg/day Boscarino: (705 patients) MED not reported	Campbell: past year pharmaceutical opioid dependence was associated with aberrant behaviors (nonadherence Adj RR 2.47, 95% CI: 1.44 to 4.24) and ICD-10 lifetime benzodiazepine dependence (Adj RR 3.22, 95% CI: 1.40 to 7.41). Other SUDs (smoking, alcohol, illicit drugs) were not significantly associated with pharmaceutical opioid dependence. Boscarino: History of opioid abuse was significantly associated with current and lifetime opioid dependence (OR 3.81 and 3.00, respectively) in multivariate models. Other SUDs (alcohol, tobacco, illicit drugs) were significant in univariate analyses but not in the multivariate models.	Very serious limitations (-2)	No serious inconsistency	No serious indirectness	No serious imprecision	Low
Aberrant results (from UDT)	1 retrospective cohort study (Turner et al. 2014)[5]	Prescription opioids (3,809 patients); MED range <40 mg/day to >120 mg/day (67.4% of patients received <40 mg/day)	Prior SUD diagnosis was weakly associated with aberrant UDT results (OR 1.42, 95% CI: 1.17 to 1.72), but alcohol use disorder was not.	Serious limitations (-1)	No serious inconsistency	No serious indirectness	No serious imprecision	Moderate
Non-adherence (prescribed opioid non-detection from UDT)			Prior SUD diagnosis was weakly associated with non-detection of prescribed opioids (OR 1.70, 95% CI: 1.31 to 2.20), but alcohol use disorder was not.					

Outcome	Quantity and Type of Evidence	Intervention (Number of Patients)	Findings	Study Limitations (Study Quality, Risk-of-Bias)[a]	Inconsistency[b]	Indirectness[c]	Imprecision[d]	GRADE of Evidence for Outcome
Opioid-related respiratory/CNS depression or overdose	1 retrospective nested case-control study (Zedler et al. 2014)[13]	Prescription opioids (8,987 veterans), mean MED for cases: 98.7 mg/day; for controls: 24.2 mg/day	History of opioid dependence was significantly associated with opioid-related toxicity/overdose (OR 3.9, 95% CI: 2.6 to 5.8). Other substance abuse and non-opioid substance dependence had a weak association with the outcome (OR 1.4, 95% CI: 1.0 to 1.8).	Very serious limitations (-2)	No serious inconsistency	No serious indirectness	No serious imprecision	Low
Overdose	1 retrospective cohort study (Turner and Liang 2015)[4]	Prescription opioids (206,869 patients); MED range 0 to >100 mg/day	Alcohol or other drug abuse was significantly related to overdose in the initial model but not in the final adjusted multivariate model.	Serious limitations (-1)	No serious inconsistency	No serious indirectness	No serious imprecision	Moderate
Opioid-related overdose death	1 case-cohort study (Bohnert et al. 2011)[12]	Codeine, morphine, oxycodone, hydrocodone, oxymorphone and hydro-morphone (155,434 patients), MED range 0 to >100 mg/day	SUD diagnosis was significantly associated with increased risk of overdose death in CNCP patients (HR 2.53, 95% CI: 1.99 to 3.22) and cancer patients (HR 3.08, 95% CI: 1.73 to 5.51)	Serious limitations (-1)	No serious inconsistency	No serious indirectness	No serious imprecision	Moderate
Suicide attempts	1 retrospective cohort study (Im et al. 2015)[3]	CSA and LA opioids (487,462 patients), dose not reported	Drug-use disorder and alcohol use disorder were significantly associated with suicide attempts for patients on CSA and LA opioids (OR 2.42 and 2.83 for drug use, 1.99 and 1.87 for alcohol use)	Serious limitations (-1)	No serious inconsistency	No serious indirectness	No serious imprecision	Moderate

Outcome	Quantity and Type of Evidence	Intervention (Number of Patients)	Findings	Study Limitations (Study Quality, Risk-of-Bias)[a]	Inconsistency[b]	Indirectness[c]	Imprecision[d]	GRADE of Evidence for Outcome
Depression or History of Depression								
Pain severity	1 post hoc analysis of RCT data (Yarlas et al. 2015)[14]	BTDS or placebo (541 patients); 10 or 20 µg/hour	Depression had no significant effect on pain severity (Cohen's d=0.13, p>0.05)	Very serious limitations (-2)	No serious inconsistency	No serious indirectness	Serious imprecision (-1) (Study may have lacked power to detect small effects)	Very Low
Pain interference			Depression had a small but significant negative impact on pain interference (Cohen's d=0.29, p<0.01).	Very serious limitations (-2)	No serious inconsistency	No serious indirectness	No serious imprecision	Low
QOL			Depression had no significant effect on health-related QOL (Cohen's d ranged from 0.06 to 0.17 for various domains)	Very serious limitations (-2)	No serious inconsistency	No serious indirectness	Serious imprecision (-1) (Study may have lacked power to detect small effects)	Very Low
Function (measured by ODI)			Depression had no significant effect on function (Cohen's d=0.08, p>0.05)	Very serious limitations (-2)	No serious inconsistency	No serious indirectness	Serious imprecision (-1) (Study may have lacked power to detect small effects)	Very Low
Sleep quality	1 post hoc analysis of RCT data (Yarlas et al. 2015)[14]	BTDS or placebo (541 patients); 10 or 20 µg/hour	Depression had no significant effect on sleep quality (Cohen's d ranged from 0.01 to 0.13 for various domains)	Very serious limitations (-2)	No serious inconsistency	No serious indirectness	Serious imprecision (-1) (Study may have lacked power to detect small effects)	Very Low

Outcome	Quantity and Type of Evidence	Intervention (Number of Patients)	Findings	Study Limitations (Study Quality, Risk-of-Bias)[a]	Inconsistency[b]	Indirectness[c]	Imprecision[d]	GRADE of Evidence for Outcome
Current opioid dependence	2 cross-sectional cohort studies (Campbell et al. 2015;[10] Boscarino et al. 2010)[11])	Prescription opioids (1,424 patients); median MED 75 (95% CI: 36 to 145) mg/day Boscarino: (705 patients) MED not reported	Campbell: Depression was not significantly associated with pharmaceutical opioid dependence in the multivariate analyses. Boscarino: History of major depression was weakly associated with current opioid dependence (OR=1.29, p=0.022) in a multivariate model	Very serious limitations (-2)	Serious inconsistency (-1)	No serious indirectness	No serious imprecision	Very Low
Lifetime opioid dependence	1 cross-sectional study (Boscarino et al. 2010)[11]	Prescription opioids (705 patients) MED not reported	History of major depression was significantly associated with lifetime opioid dependence in a univariate comparison but not in a multivariate model.	Very serious limitations (-2)	No serious inconsistency	No serious indirectness	No serious imprecision	Low
Opioid-related respiratory/CNS depression or overdose	1 retrospective nested case-control study (Zedler et al. 2014)[13]	Prescription opioids (8,987 veterans), mean MED for cases:98.7 mg/day; for controls: 24.2 mg/day	History of depression was not significantly associated with opioid-related toxicity/overdose (OR 1.2, 95% CI: 1.0 to 1.5, p=0.105).	Very serious limitations (-2)	No serious inconsistency	No serious indirectness	Serious imprecision (-1)	Very Low
Overdose	1 retrospective cohort study (Turner and Liang 2015)[4]	Prescription opioids (206,869 patients); MED range 0 to >100 mg/day	In the interaction between opioid therapy and depression, the adjusted odds of overdose were significantly higher for persons with depression than those without this diagnosis, regardless of opioid dose (all p<0.001).	Serious limitations (-1)	No serious inconsistency	No serious indirectness	No serious imprecision	Moderate

Outcome	Quantity and Type of Evidence	Intervention (Number of Patients)	Findings	Study Limitations (Study Quality, Risk-of-Bias)[a]	Inconsistency[b]	Indirectness[c]	Imprecision[d]	GRADE of Evidence for Outcome
Mood Disorders								
Suicide attempts	1 retrospective cohort study (Im et al. 2015)[3]	CSA and LA opioids (487,462 patients), dose not reported	Mood disorders were significantly associated with suicide attempts for patients on CSA and LA opioids (OR 3.5 and 3.9, respectively)	Serious limitations (-1)	No serious inconsistency	No serious indirectness	No serious imprecision	Moderate
Borderline Personality Disorder								
Lifetime opioid dependence	1 cross-sectional cohort study (Campbell et al. 2015)[9]	Prescription opioids (978 patients); median MED 75 (95% CI: 37.5 to 150) mg/day	BPD was independently associated with lifetime pharmaceutical opioid dependence (OR 2.49, 95% CI: 1.42 to 4.38) in a multivariate analysis.	Very serious limitations (-2)	No serious inconsistency	No serious indirectness	No serious imprecision	**Low**
12-month suicidal ideation			People with BPD had 2.9 times the odds of experiencing past 12-month suicidal ideation ($p<0.001$).					
Lifetime suicide attempts			People with BPD had 3.2 times the odds of experiencing a lifetime suicide attempt ($p<0.001$)					
Other outcomes			Pain severity, pain interference, non-adherence, opioid medication problems, and lifetime accidental overdose were not significantly associated with BPD.					
Opioid-related respiratory/CNS depression or overdose	1 retrospective nested case-control study (Zedler et al. 2014)[13]	Prescription opioids (8,987 veterans), mean MED for cases:98.7 mg/day; for controls: 24.2 mg/day	History of BPD had a weak association with opioid-related toxicity/overdose (OR 1.7, 95% CI: 1.2 to 2.4).	Very serious limitations (-2)	No serious inconsistency	No serious indirectness	No serious imprecision	Low

Outcome	Quantity and Type of Evidence	Intervention (Number of Patients)	Findings	Study Limitations (Study Quality, Risk-of-Bias)[a]	Inconsistency[b]	Indirectness[c]	Imprecision[d]	GRADE of Evidence for Outcome
Antisocial Personality Disorder								
Opioid dependence (current or lifetime)	1 cross-sectional cohort study (Boscarino et al. 2010)[11]	Prescription opioids (705 patients) MED not reported	History of antisocial personality disorder was weakly associated with lifetime opioid dependence in a multivariate model (OR=1.44, p=0.015). It was not associated with current opioid dependence in a multivariate model.	Very serious limitations (-2)	No serious inconsistency	No serious indirectness	No serious imprecision	Low
Generalized Anxiety Disorder or PTSD								
Opioid dependence	2 cross-sectional cohort studies (Campbell et al. 2015[10]; Boscarino et al. 2010)[11])	Prescription opioids: Campbell: (1,424 patients); median MED 75 (95% CI: 36 to 145) mg/day Boscarino: (705 patients) MED not reported	Anxiety and PTSD were not significantly associated with opioid dependence in multivariate analyses (Boscarino had shown an association in univariate analyses but not in the final multivariate analyses).	Very serious limitations (-2)	No serious inconsistency	No serious indirectness	No serious imprecision	Low
Opioid-related respiratory/CNS depression or overdose	1 retrospective nested case-control study (Zedler et al. 2014)[13]	Prescription opioids (8,987 veterans), mean MED for cases:98.7 mg/day; for controls: 24.2 mg/day	Neither anxiety nor PTSD were significantly associated with opioid-related toxicity/overdose (OR 1.1 and 1.0, respectively).	Very serious limitations (-2)	No serious inconsistency	No serious indirectness	No serious imprecision	Low
Drug overdose	1 retrospective cohort study (Turner and Liang 2015)[4]	Prescription opioids (206,869 patients); MED range 0 to >100 mg/day	Anxiety/PTSD diagnosis was not significantly associated with drug overdose	Serious limitations (-1)	No serious inconsistency	No serious indirectness	No serious imprecision	Moderate

Outcome	Quantity and Type of Evidence	Intervention (Number of Patients)	Findings	Study Limitations (Study Quality, Risk-of-Bias)[a]	Inconsistency[b]	Indirectness[c]	Imprecision[d]	GRADE of Evidence for Outcome
Opioid-related accident/ overdose	1 retrospective cohort study (Seal et al. 2012)[8]	Prescription opioids (15,676 patients)	PTSD with or without other mental health diagnoses was not significantly associated with opioid-related accident/overdose compared to patients with other mental health diagnoses. However, accident/overdose was significantly associated with the PTSD group when compared to patients with no mental health diagnosis (p<0.001).	Very serious limitations (-2)	No serious inconsistency	No serious indirectness	No serious imprecision	Low
Alcohol and nonopioid drug-related accidents/ overdose			PTSD with or without other mental health diagnoses was significantly associated with increased risk of alcohol and nonopioid drug-related accident/overdose (p<0.001)					
Self-inflicted injuries (e.g., suicide attempt)			PTSD with or without other mental health diagnoses was significantly associated with increased risk of self-inflicted injuries (p<0.001).					
Wounds/injuries, violence-related injuries			PTSD with or without other mental health diagnoses was not significantly associated with increased risk of wounds or violence-related injuries.					
Psychotic Disorder								
Drug overdose	1 retrospective cohort study (Turner and Liang 2015)[4]	Prescription opioids (206,869 patients); MED range 0 to >100 mg/day	Psychotic disorder was not significantly associated with drug overdose	Serious limitations (-1)	No serious inconsistency	No serious indirectness	No serious imprecision	Moderate

Outcome	Quantity and Type of Evidence	Intervention (Number of Patients)	Findings	Study Limitations (Study Quality, Risk-of-Bias)[a]	Inconsistency[b]	Indirectness[c]	Imprecision[d]	GRADE of Evidence for Outcome
Negative Affect								
Average daily pain improvement	1 prospective cohort study (Wasan et al. 2015)[1]	Morphone or oxycodone (55 patients); mean MED 75.6 to 94.7 mg/day	The high NA group had a significantly smaller average improvement in pain than the low NA group (21% vs. 39%, p<0.01).	Serious limitations (-1)	No serious inconsistency	No serious indirectness	Serious imprecision (-1) (1 small study)	Low
Opioid misuse			The high NA group had a significantly greater rate of opioid misuse than the low NA group (39% vs. 8%, p=0.013)					
Adverse effects			The high NA group had significantly more and intense opioid side effects than the low NA group (p=0.0001).					
Psychiatric Disorders (Excluding Substance Use Disorders)								
Aberrant results (from UDT)	1 retrospective cohort study (Turner et al. 2014)[5]	Prescription opioids (3,809 patients); MED range <40 mg/day to >120 mg/day (67.4% of patients received <40 mg/day)	Mental health diagnosis was not significantly associated with aberrant UDT results (OR 1.11, 95% CI: 0.96 to 1.27)	Serious limitations (-1)	No serious inconsistency	No serious indirectness	No serious imprecision	Moderate
Non-adherence (prescribed opioid non-detection from UDT)			Mental health diagnosis was not significantly associated with prescribed opioid non-detection (OR 1.19, 95% CI: 0.99 to 1.44).					
Overdose deaths	1 case-cohort study (Bohnert et al. 2011)[12]	Codeine, morphine, oxycodone, hydrocodone, oxymorphone and hydro-morphone (155,434 patients), MED range 0 to >100 mg/day	Psychiatric disorders diagnosis was weakly associated with increased risk of overdose death in CNCP patients (HR 1.87, 95% CI: 1.48 to 2.38) but not in cancer patients (HR 1.68, 95% CI: 0.95 to 3.00)	Serious limitations (-1)	No serious inconsistency	No serious indirectness	No serious imprecision	Moderate

Outcome	Quantity and Type of Evidence	Intervention (Number of Patients)	Findings	Study Limitations (Study Quality, Risk-of-Bias)[a]	Inconsistency[b]	Indirectness[c]	Imprecision[d]	GRADE of Evidence for Outcome
Psychiatric Disorders (Excluding PTSD)								
Opioid-related accidents and overdoses, alcohol and non-opioid related accidents and overdoses, and self-inflicted injuries	1 retrospective cohort study (Seal et al. 2012)[8]	Prescription opioids (15,676 patients), MED not reported	Opioid users with non-PTSD mental health disorders had significantly higher rates of all of these events compared to opioid users with no mental health disorders (p<0.001).	Very serious limitations (-2)	No serious inconsistency	No serious indirectness	No serious imprecision	Low
Wounds/injuries, violence-related injuries			There was no significant difference in these outcomes for patients with and without mental health disorders.					
Traumatic Brain Injury (TBI)								
Suicide attempts	1 retrospective cohort study (Im et al. 2015)[3]	CSA and LA opioids (487,462 patients), dose not reported	TBI was weakly associated with suicide attempts for patients on CSA and LA opioids (OR 1.31 and 1.5, respectively)	Serious limitations (-1)	No serious inconsistency	No serious indirectness	No serious imprecision	Moderate
Charlson Score/Medical Frailty								
Opioid use disorder (abuse or dependence)	1 retrospective cohort study (Edlund et al. 2014)[6]	Short-acting and/or long-acting opioids (568,640 patients); MED range 0 to >120 mg/day	Charlson score was not significantly associated with opioid use disorder in multiple regression models.	Serious limitations (-1)	No serious inconsistency	No serious indirectness	No serious imprecision	Moderate
Suicide attempts	1 retrospective cohort study (Im et al. 2015)[3]	CSA and LA opioids (487,462 patients), dose not reported	Medical frailty was not significantly associated with suicide attempts for CSA and LA opioids	Serious limitations (-1)	No serious inconsistency	No serious indirectness	No serious imprecision	Moderate

Outcome	Quantity and Type of Evidence	Intervention (Number of Patients)	Findings	Study Limitations (Study Quality, Risk-of-Bias)[a]	Inconsistency[b]	Indirectness[c]	Imprecision[d]	GRADE of Evidence for Outcome
Congestive Heart Failure Diagnosis/Use of QT-prolonging Medications								
Cardiac events	1 retrospective cohort study (Price et al. 2014)[7]	Methadone (1,246 patients); chronic users had a median dose of 30 mg, while non-chronic users had a median dose of 15 mg	CHF diagnosis and use of QT-prolonging medications were not significantly associated with cardiac events.	Serious limitations (-1)	No serious inconsistency	No serious indirectness	No serious imprecision	Moderate
Diagnosis of COPD or Sleep Apnea								
Opioid-related respiratory/CNS depression or overdose	1 retrospective nested case-control study (Zedler et al. 2014)[13]	Prescription opioids (8,987 veterans), mean MED for cases:98.7 mg/day; for controls: 24.2 mg/day	History of COPD was weakly associated with opioid-related toxicity/overdose (OR 1.5, 95% CI: 1.2 to 1.9). Sleep apnea also had a weak association with the outcome (OR 1.3, 95% CI: 1.0 to 1.8).	Very serious limitations (-2)	No serious inconsistency	No serious indirectness	No serious imprecision	Low
Overdose deaths	1 case-cohort study (Bohnert et al. 2011)[12]	Codeine, morphine, oxycodone, hydrocodone, oxymorphone and hydro-morphone (155,434 patients), MED range 0 to >100 mg/day	Diagnosis of COPD, CVD or sleep apnea was weakly associated with reduced risk of overdose-related death for patients with CNCP (HR 0.63, 95% CI: 0.50 to 0.80). The effect did not reach statistical significance for patients with cancer (HR 0.73, 95% CI: 0.38 to 1.42).	Serious limitations (-1)	No serious inconsistency	No serious indirectness	No serious imprecision	Moderate

Outcome	Quantity and Type of Evidence	Intervention (Number of Patients)	Findings	Study Limitations (Study Quality, Risk-of-Bias)[a]	Inconsistency[b]	Indirectness[c]	Imprecision[d]	GRADE of Evidence for Outcome
Cognitive Impairment								
Opioid-related respiratory/CNS depression or overdose	1 retrospective nested case-control study (Zedler et al. 2014)[13]	Prescription opioids (8,987 veterans), mean MED for cases:98.7 mg/day; for controls: 24.2 mg/day	History of dementia was not significantly associated with opioid-related toxicity/overdose (OR 1.0, 95% CI: 0.3 to 3.1)	Very serious limitations (-2)	No serious inconsistency	No serious indirectness	Serious imprecision (-1) (Wide 95% CI: around the OR includes possibility of association)	Very Low
Renal Disease								
Opioid-related respiratory/CNS depression or overdose	1 retrospective nested case-control study (Zedler et al. 2014)[13]	Prescription opioids (8,987 veterans), mean MED for cases:98.7 mg/day; for controls: 24.2 mg/day	Renal disease was weakly associated with opioid-related toxicity/overdose (OR 1.7, 95% CI: 1.3 to 2.4)	Very serious limitations (-2)	No serious inconsistency	No serious indirectness	No serious imprecision	Low
Liver Disease								
Opioid-related respiratory/CNS depression or overdose	1 retrospective nested case-control study (Zedler et al. 2014)[13]	Prescription opioids (8,987 veterans), mean MED for cases:98.7 mg/day; for controls: 24.2 mg/day	Mild liver disease was not significantly associated with opioid-related toxicity/overdose (OR 1.6, 95% CI: 0.9 to 3.2). The same is true for viral hepatitis (OR 1.4, 95% CI: 0.9 to 2.0).	Very serious limitations (-2)	No serious inconsistency	No serious indirectness	Serious imprecision (-1) (Wide 95% CI: around the OR includes possibility of weak association)	Very Low

Outcome	Quantity and Type of Evidence	Intervention (Number of Patients)	Findings	Study Limitations (Study Quality, Risk-of-Bias)[a]	Inconsistency[b]	Indirectness[c]	Imprecision[d]	GRADE of Evidence for Outcome
Pancreatitis								
Opioid-related respiratory/CNS depression or overdose	1 retrospective nested case-control study (Zedler et al. 2014)[13]	Prescription opioids (8,987 veterans), mean MED for cases:98.7 mg/day; for controls: 24.2 mg/day	Pancreatitis was significantly associated with opioid-related toxicity/overdose (OR 2.2, 95% CI: 1.1 to 4.5)	Very serious limitations (-2)	No serious inconsistency	No serious indirectness	No serious imprecision	Low

[a] Methodological Quality takes into account the overall risk of bias rating of all the studies included in the evidence base;

[b] Inconsistency of results considers if the studies demonstrated similar positive or negative results (an inconsistent rating would indicate that the findings across studies were mixed);

[c] Indirectness of evidence considers the link between the interventions and patient outcomes (head-to-head comparisons provide the most direct evidence) as well as the applicability of the study population; and

[d] Imprecision estimates the degree of uncertainty (based on variance or sample size) around an outcome's effect size.

BPD: borderline personality disorder; BPI: brief pain inventory; BTDS: buprenorphine transdermal system; CHF: congestive heart failure; CI: confidence interval; CLBP: chronic low back pain; CNCP: chronic non-cancer pain; CNS: central nervous system; COPD: chronic obstructive pulmonary disease; COT: chronic opioid therapy; CSA: chronic short-acting; CVD: cardiovascular disease; HR: hazard ratio; LA: long-acting; MED: morphine equivalent dose; mg: milligram; NA: negative affect; ODI: Oswestry Disability Index; OUD: opioid use disorder; OR: odds ratio; PTSD: posttraumatic stress disorder; RCT: randomized controlled trial; RR: relative risk; SD: standard deviation; SUD: substance use disorder; TBI: traumatic brain injury; TOA: therapeutic opioid addiction; UDT: urine drug test

Appendix A. Evidence Tables

Table 2. Individual Studies

Study Details	Patients/Interventions	Methods	Outcomes/Results
Reference: Campbell et al. 2015[10] **Country:** Australia **Study Design:** Cross-sectional cohort study **Purpose:** 1) Describe levels of current pharmaceutical opioid consumption, and the correlates of different levels of consumption; 2) Examine the prevalence of lifetime dependence and past year dependence as per ICD-10 criteria; and 3) Examine the correlates of the criteria met for pharmaceutical opioid dependence. **Quality Rating:** Poor Patients eligible but not participating were not compared with those who participated, so generalizability is unclear. Patients who did not provide OME data had more comorbidities than patients who provided OME data. All variables and outcomes were measured at the same time, so causality could not be determined. Study did not control for all relevant comorbidities, but did use multivariate analyses to adjust for several relevant variables.	**Number of Patients:** 1,424 **Diagnosis:** CNCP **Age (Years):** Median 58 years **Gender:** 55% female **Inclusion Criteria:** 18 years of age or older; fluent in English; mentally and physically able to complete telephone and self-complete interviews; without obvious cognitive impairment; living with CNCP; prescribed an opioid such as morphine, oxycodone, or fentanyl; and having taken such opioids for CNCP for more than 6 weeks. **Exclusion Criteria:** Those currently prescribed methadone or buprenorphine as opioid substitution therapy for heroin dependence or taking opioids for cancer pain were not eligible.	OME was determined through medication diaries (only 1,085 patients returned these). Opioid dependence was determined by interviews (1,424 patients completed the CIDI to determine ICD-10 dependence). OME groups were compared using multinomial logistic regression; relative risk ratios, and 95% CIs were used for proportions. The category of 21–90 mg/day OME was used as the reference group in the multinomial regressions, as this range represented usual therapeutic doses and the largest group in the sample. Two groups were defined according to whether or not they met ICD-10 criteria for pharmaceutical opioid dependence in the past year. Univariate logistic regression models were conducted to compare these groups. Relative risk and Hedges g are reported with 95% CI; a multivariate model was also conducted to determine the independence of associations of variables significant in bivariate analyses; these factors include age, gender, employment status, median number of pain conditions, pain interference score, PSEQ score, nonadherence, substance use (4 categories), depression, generalized anxiety disorder, and PTSD. Adjusted RR and 95% CI: are reported. **Follow-up:** One year (for symptom occurrence prior to interview)	**Opioid Dependence Risk Factors:** In the multivariate analyses, patients with past year pharmaceutical opioid dependence were: 1) younger (Adj RR 0.97, 95% CI: 0.95-0.99); 2) more likely to engage in aberrant behaviors (nonadherence Adj RR 2.47, 95% CI: 1.44-4.24); and 3) more likely to meet criteria for ICD-10 lifetime benzodiazepine dependence (Adj RR 3.22, 95% CI: 1.40–7.41). The authors ran a post hoc multivariate analysis including OME which resulted in: 1) age (RR 0.96, 95% CI: 0.93–0.99); 2) aberrant behaviors (RR 2.49, 95% CI: 1.18–5.24); and 3) ICD-10 lifetime benzodiazepine dependence (RR 4.31, 95%CI 1.55–12.63) remaining significant. Other substance abuse (smoking, alcohol, illicit drugs) and mental health conditions (depression, anxiety, PTSD) were not significantly associated with pharmaceutical opioid dependence in the multivariate analyses. In univariate analyses, OME ≥200 mg/day was significantly associated with pharmaceutical opioid dependence (lifetime and past 12 months), past 3 month tampering, illicit drug use, increased pain scores, and moderate-severe depression.

Study Details	Patients/Interventions	Methods	Outcomes/Results
Reference: Campbell et al. 2015[9] **Country:** Australia **Study Design:** Cross-sectional cohort study **Purpose:** To examine the prevalence and associations of BPD in a large community sample of CNCP patients and the association with medication problems and suicidality. **Quality Rating:** Poor Patients eligible but not participating were not compared with those who participated, so generalizability is unclear. All variables and outcomes were measured at the same time, so causality could not be determined. IPDE tool used to identify BPD is a screening tool but not a diagnostic tool. Study did not control for all relevant comorbidities, but did use multivariate analyses to adjust for several relevant variables.	**Number of Patients:** 978 **Diagnosis:** CNCP **Age (Years):** mean (57.5 (SD 13.6) years **Gender:** 44.7% male **Inclusion Criteria:** Participants were eligible if they were 18 years or older, competent in English, mentally and physically able to partake in telephone and self-complete interviews, without serious cognitive impairments, living with chronic non-cancer pain (CNCP) and taking prescribed Schedule 8 opioids (morphine, oxycodone, buprenorphine, methadone and hydromorphone) for CNCP for more than 6 weeks. **Exclusion Criteria:** People currently prescribed pharmaceutical opioids for opioid substitution therapy for heroin dependence or for cancer were not eligible.	Of the 1514 participants enrolled in the POINT study, 978 completed the BPD module. The BPD screener was adapted from the IPDE. Suicidality was defined in current study as thoughts or attempts. In hierarchical regression models, due to small numbers, lifetime accidental overdose (n=163) was used instead of past 12-month overdose (n=25), and lifetime suicide attempts (n=192) were used instead of past 12-month attempts (n=22). Past 12-month suicidal ideation was used (n=193). Hierarchical regression models were conducted to examine whether BPD was independently associated with pain severity, interference, medication non-adherence, overdose, lifetime pharmaceutical opioid dependence, past 12-month suicidal thoughts and lifetime suicide attempts after controlling for the following: model 1: sociodemographic factors (age, sex, unemployed); model 2: sociodemographic factors, pain-related factors (time in pain, number of chronic conditions, lifetime or past 12-month presence of arthritis, chronic back/neck problems, frequent headaches/migraines, visceral pain, fibromyalgia, pain severity, pain interference, SF12 physical health score); model 3: sociodemographic factors, pain-related factors, mental health (lifetime/12-month major depression, lifetime/12- month GAD, lifetime/12-month PTSD); model 4: sociodemographic factors, pain-related factors, mental health, substance use (lifetime alcohol use disorder, lifetime drug use disorders). The hierarchical regressions were based on a reduced sample size of 749, based on the people who had returned their medication diaries and self-complete surveys. **Follow-up:** one year (for symptom occurrence prior to interview)	**BPD was independently associated with lifetime pharmaceutical opioid dependence:** (OR 2.49, 95% CI: 1.42–4.38) after adjusting for demographics, pain-related factors, mental health and lifetime alcohol and illicit substance use dependence. **BPD was independently associated with past 12-month suicidal ideation and lifetime suicide attempts:** After adjusting for age, gender, unemployment, pain-related factors, mental health and substance use, people with BPD had 2.9 times the odds of experiencing past 12-month suicidal ideation and 3.2 times the odds of experiencing a lifetime suicide attempt. Pain severity, pain interference, non-adherence, opioid medication problems, and lifetime accidental overdose were not significantly associated with BPD.

Study Details	Patients/Interventions	Methods	Outcomes/Results
Reference: Huffman et al. 2015[2] **Country:** USA **Study Design:** Retrospective cohort study **Purpose:** To examine the associations of non-opioid substance use disorders, opioid dosage, and TOA in a population of patients thought to be representative of those at highest risk. **Quality Rating:** Fair Several relevant confounders were not adjusted for in the logistic regression; included patients did not differ significantly from excluded patients in demographics or history of SUD.	**Number of Patients:** 199 **Diagnosis:** CNCP **Age (Years):** Mean 46.5 (±13.6) years **Gender:** 60.8% female **Inclusion Criteria:** Cases were included in the study if patients 1) were undergoing long-term opioid therapy at the time of admission or 2) had been weaned from opioids as part of chemical dependency treatment (or by virtue of running out of opioids) directly before admission. **Exclusion Criteria:** Patients were excluded if 1) they had a history of nonmedicinal opioid use that preceded the introduction of therapeutic opioids; 2) they had abused therapeutic opioids but did not meet full criteria for TOA; or 3) the diagnosis of TOA could not be excluded or made conclusively.	All patients had undergone long-term opioid therapy before starting the study. The study treatment was a chronic pain rehabilitation program (5 days/week, 8 hrs/day for 3 to 4 weeks) that included weaning of opioids and other addictive medications, individual and group psychotherapy, physical therapy, occupational therapy, substance use education and monthly aftercare. A binary logistic regression, including gender and age as controls, was used to determine whether a lifetime history of a non-opioid substance use disorder or morphine equivalence dosage at time of admission predicted increased odds of having TOA. **Follow-up:** 3 to 4 weeks	**Risk Factors for TOA**. The final model found (after adjustment for age and gender): 1) lifetime history of an SUD was associated with 28 times increased odds of TOA (OR=28.5; 95% CI: 10.86, 75.27); and 2) opioid dose was associated with TOA. Each 10-mg increase of oral morphine was associated with a 12% increase in odds of TOA (OR=1.12; 95% CI: 1.05, 1.18). Each 50-mg increase was associated with a 73% increase in odds of TOA (OR=1.73; 95% CI: 1.29, 2.32). Each 100-mg increase was associated with 3-fold increase in odds of TOA (OR=3.00; 95% CI: 1.67, 5.41) after adjustment for age and gender. Gender and age were not significantly associated with TOA.
Reference: Im et al. 2015[3] **Country:** USA **Study Design:** Retrospective cohort study **Purpose:** To examine associations between the receipt of guideline-recommended care for opioid therapy and risk of suicide attempt. **Quality Rating:** Fair Very large population included; multiple relevant variables included in analysis, but a few relevant potential confounders not included; for certain	**Number of Patients:** 487,462 veterans **Diagnosis:** Not reported; 80.8% received CSA opioids, 19.2% received LA opioids **Age (Years):** ≥18 years, mean and range not reported **Gender:** 93.5% male **Inclusion Criteria:** All Veteran patients prescribed any short-acting opioids on a chronic basis (chronic short-acting) or any long-acting opioids from the VHA during fiscal year 2010 (FY10) were included in this analysis. Chronic use of short-acting opioids was defined as having at least 90 days of supply in FY10. **Exclusion Criteria:** Not reported	Multivariate, mixed-effects logistic regression analyses were conducted to define the associations between the risk of suicide attempt and receipt of guideline-recommended care at the individual level and rates of use of recommended care at the facility level, while accounting for patient risk factors. Separate analyses were done for patients receiving CSA opioids and patients receiving LA opioids, respectively. Individual-level variables included age, gender, and marital status. Age was categorized into three groups: younger than 31 years old, 31–55 years old, and greater than 55 years old. Physical/mental health status was represented by indicator variables for medical frailty, drug/alcohol/mood disorder, and traumatic brain injury. Binary indicator variables were used to identify whether	**CSA Opioid Therapy: Multivariate Logistic Regression Analysis for Risk of Suicide Attempts** At the individual level, suicide attempts were associated with being younger, female, currently unmarried, and having medical frailty, drug/alcohol/mood disorder, or traumatic brain injury. In particular, having a mood disorder was highly associated with suicide attempts (OR=3.5, 95% CI: 3.3–3.9). Moreover, patients receiving psychosocial assessment/therapy, sedative co-prescription, drug screening, medication management, rehabilitation medicine, and anti-inflammatory or specialty pain pharmacotherapy were associated with increased risk of suicide attempt.

Study Details	Patients/Interventions	Methods	Outcomes/Results
independent variables (e.g., mood disorder), it could not be determined if the diagnosis preceded the suicide attempt.		patients received guideline-recommended care. Facility-level guideline-recommended care delivery rates were also used in the analysis. These rates were calculated for each VHA facility by dividing the number of patients on opioid therapy receiving each guideline recommended service by the total number of patients on opioid therapy within the VHA facility. **Follow-up:** 180 days following prescription initiation	At the facility-level, patients prescribed CSA opioid therapy within VHA facilities ordering more drug screens were associated with decreased risk of suicide attempt (OR=0.2, 95% CI=0.1–0.3). SUD subgroup: In general, the pattern of individual-level findings was similar for the subset of CSA patients with an SUD diagnosis. At the facility-level, SUD-diagnosed patients on CSA opioid therapy within VHA facilities ordering regular drug screens (defined as at least one drug screen for every 90 days of opioid supply) more consistently or providing more SUD specialty treatment/SUD specific pharmacotherapies were associated with decreased risk of suicide attempt (ORs=0.3, 95% CI: 0.2–0.6). **LA Opioid Therapy: Multivariate Logistic Regression Analysis for Risk of Suicide Attempts** For the entire LA opioid therapy group, suicide attempts were associated with being younger, currently unmarried, and having medical frailty, drug/alcohol/mood disorder, or traumatic brain injury. Similarly, having a mood disorder was highly associated with suicide attempts (OR=3.9, 95% CI=3.3–4.6). Patients receiving psychosocial assessment/therapy, sedative co-prescription, drug screening, medication management, rehabilitation medicine, or specialty pain pharmacotherapy were associated with increased risk of suicide attempt. At the facility level, the LA opioid therapy group within VHA facilities ordering more drug screens was associated with decreased risk of suicide attempt (OR=0.3, 95% CI=0.2–0.6); in addition, the LA opioid therapy group within VHA facilities providing more follow-up after new prescriptions was associated with decreased risk of suicide attempt (OR=0.2,

Study Details	Patients/Interventions	Methods	Outcomes/Results
			95% CI=0.0–0.7), and the LA opioid therapy group within VHA facilities having higher sedative co-prescription rates was associated with increased risk of suicide attempt (OR=20.3, 95% CI=1.1–382.2). SUD subgroup: For the SUD-diagnosed group on LA opioid therapy, the pattern of individual-level findings was identical to those for the entire LA group, except that being currently unmarried was not associated with suicide attempts for patients with SUD. At the facility-level, SUD-diagnosed group on LA opioid therapy within VHA facilities providing more rehabilitation medicine were associated with decreased risk of suicide attempt (OR=0.3, CI=0.1–0.9), while SUD diagnosed patients within VHA facilities having higher sedative co-prescription rates and providing more SNRIs were associated with increased risk of suicide attempt (ORs=30.2 and 62.2; 95% CIs=1.1–829.3 and 2.2–1,769.3, respectively).
Reference: Turner and Liang 2015[4] **Country:** USA **Study Design:** Retrospective cohort study **Purpose:** To examine interactions of filled prescriptions for opioids, benzodiazepines, antidepressants, and zolpidem with mental health disorders in regard to drug overdose. **Quality Rating:** Fair Good participation and low attrition, multivariate analysis controlled for most potential confounders. Limitations	**Number of Patients:** 206,869 **Diagnosis:** Non-cancer pain **Age (Years):** Mean 44.1 (±12) years **Gender:** 57% female **Inclusion Criteria:** The study cohort included persons aged 18 to 64 years with non-cancer pain who filled at least two Schedule II or III prescriptions for non-injectable opioid analgesics from January 2009 through July 2012. Eligible subjects were continuously enrolled at least 12 months in the Aetna plan and had claims for service utilization at least 6 months before the first drug overdose event. **Exclusion Criteria:** The most frequent exclusions were due to incomplete opioid prescription data, missing diagnostic data, or a non-basal cell cancer diagnosis.	All patients received non-injectable opioid analgesics. The study outcome was drug overdose diagnosed from an inpatient or outpatient clinical encounter following the first filled opioid prescription. For each subject, this time-varying outcome was measured in each 6-month interval after the first filled opioid prescription until last enrollment or end of the study time frame. Using repeated-measures logistic regression with the generalized estimating equations method under an unstructured correlation matrix, the authors examined the effects of daily opioid dose and duration of filled prescriptions for psychoactive drugs on the odds of overdose, adjusting for time-fixed covariates (i.e., age, sex, and region) as well as time-varying covariates (i.e., chronic pain	**Risk Factors for Drug Overdose**. In the fully adjusted model, the following significant interactions were observed: 1) opioid therapy with depression (chi(4)=36.53, p<0.001); 2) antidepressant therapy with depression (chi(3)=20.20, p<0.001); 3) benzodiazepine therapy with anxiety/PTSD (chi(3)=10.36, p=0.016) and 4) zolpidem therapy with anxiety/PTSD diagnosis (chi(3)=8.79, p=0.03). Opioid dose and depression: The adjusted odds of overdose were significantly higher for persons with depression regardless of opioid dose (all p<0.001). The AOR of drug overdose were 7.06 (95 % CI: 5.30 to 9.42) for the combined effect of depression and very high opioid dose (≥100 mg) vs. no

Study Details	Patients/Interventions	Methods	Outcomes/Results
were use of coded diagnoses with limited sensitivity for mental health disorders; adherence to prescriptions could not be determined; some overdoses may have been due to illicit drug use.		conditions, mental health, and substance use disorders). Clinical judgment guided a backward model selection procedure. The authors started with a full model including demographics, clinical conditions, substance use disorders (i.e., drug or alcohol), and medications, as well as all possible interactions of daily opioid dose with each of the three psychoactive drug groups (i.e., benzodiazepines, antidepressants, and zolpidem), and interactions of each of these drugs with mental health conditions (i.e., anxiety/PTSD, depression, and psychotic disorder). The final model included clinically important and/or statistically significant factors. **Follow-up:** 3.5 years	depression or opioid use. An increasing opioid dose monotonically increased the likelihood of drug overdose (chi2(4)=24.20, p<0.001) with AOR 1.78, (95% CI: 1.39 to 2.29) for a very high opioid dose vs no opioids. Opioid dose in persons without depression: drug overdose was associated with increasing opioid dose (chi2(4)=161.4, p<0.001), but the risk rose gradually with all but a very high daily dose (AOR 4.34, 95 % CI: 3.37 to 5.57) vs no opioids. Longer-term antidepressants (91–180 days) were protective for persons with depression, with 20% lower AORs for overdose versus short-term (1–30 days) or none. For persons without depression, the AORs of overdose were increased for antidepressant use, but greatest (AOR 1.98) for short-term use versus none. Benzodiazepine therapy: The AORs of overdose increased with duration of benzodiazepine among all subjects, with >2.5-fold higher AORs for 91–180 days vs. none.
Reference: Wasan et al. 2015[1] **Country:** USA **Study Design:** Prospective cohort study **Purpose:** To understand prospectively and longitudinally whether high NA (an indicator of psychiatric comorbidity) is associated with treatment failure in CLBP patients initiating treatment with opioids **Quality Rating:** Fair	**Number of Patients:** 81 patients enrolled, 55 had data suitable for analysis at follow-up. **Diagnosis:** CLBP **Age (Years):** Low NA: mean 55 years; moderate NA: mean 54 years; high NA: mean 49 years **Gender:** % female: low NA: 67; moderate NA 43; high NA 58 **Inclusion Criteria:** (1) age ranging from 21 to 75 yr; (2) CLBP of at least 6 months duration with an average pain score of more than 3/10 (established with a 1-week baseline pain observation period, using daily, electronic pain ratings); (3) low back	Patients received morphine or oxycodone The primary outcome measure was % improvement in average daily pain during the opioid continuation period (measured with daily pain ratings on the electronic diary and calculated on a weekly basis), in comparison with the average baseline pain level. The primary comparisons of interest were the outcomes differences between the low and the high NA groups. NA was determined by the combined depression and anxiety subscale scores of the Hospital Anxiety and Depression Scale total score. Statistical analyses were based on a "modified intent-to-treat principle," such that subjects	**NA Associations with Clinical Outcomes**. Pain improvement: Despite the high NA group being prescribed a higher average daily opioid dose (94.7 mg daily) compared to the low NA group (75.6 mg daily), the 24 study completers in each of the high NA and low NA groups had an average 21% versus 39% improvement in pain, respectively (p<0.01). Opioid misuse: The high NA group also had a significantly greater rate of opioid misuse (39% vs. 8%, p=0.013) Adverse effects: The high NA group reported significantly more and intense opioid side effects (p=0.0001).

Study Details	Patients/Interventions	Methods	Outcomes/Results
Moderate participation and high attrition rate; statistical analysis did not control for all potential confounders	pain (LBP) meeting Quebec Task Force Criteria for Grades I to III (LBP only to LBP with intermittent radicular pain [not constant or daily] and no neurologic signs);36 (4) no back surgery within the past year; (5) having degenerative disc disease as a component of a pain syndrome of mixed etiology, confirmed by history, examination, and a previous lumbar magnetic resonance imaging; (6) no opioid use or use of short-acting opioids only, and less than 90 mg/day in morphine equivalents and those subjects taking opioids must also have agreed to a 2-week opioid washout period before beginning medication; (7) no pregnancy or intent to become pregnant during the study period; (8) no intent to begin new pain or psychiatric treatments during the study (such as pain medication, nerve blocks, physical therapy, or psychiatric medication) or increase in any current medications; (9) no current, active substance use disorder and no history of an opioid substance use disorder (assessed with the Mini International Neuropsychiatric Interview);37 and (10) no active suicidality or psychosis (assessed by the Mini International Neuropsychiatric Interview as well). **Exclusion Criteria:** Not reported	had to complete at least 50% of the opioid treatment period to have their data included for analysis. LMM was used to compare the low NA versus high NA groups over time. LMM "borrows" information pertaining to the relationship between the weekly outcomes, such that subjects missing some weekly data (but not all) can still be used for analyses. To further address the possible impacts of missing data (those who completed at least 50% but not 100% of the opioid treatment period), the authors imputed data using Last Observation Carried Forward and Baseline Observation Carried Forward methods as part of a secondary, sensitivity analysis. **Follow-up:** 6.5 months	Pain interference: The low NA group also reported significantly greater change in pain interference (items 9A to G of the BPI, which includes general activity, walking, work, sleep, and social relations, p=0.0001), and Global impression of change: The low NA group reported "much improved" global impression of change versus "minimally improved" in the high NA group (p=0.026).
Reference: Yarlas et al. 2015[14] **Country:** USA **Study Design:** Post hoc analysis of RCT data **Purpose:** To examine whether worse post-treatment outcomes for depressed patients with CLBP are driven by reduced treatment efficacy	**Number of Patients:** 541 **Diagnosis:** CLBP **Age (Years):** Mean 49.5 years **Gender:** 55% female **Inclusion Criteria:** Not reported **Exclusion Criteria:** Not reported	Patients received BTDS or placebo. Patient characteristics and baseline values of outcome measures were statistically compared between depressed and non-depressed patients. Outcomes of interest included pain severity, pain interference, quality of life, sleep quality, and functional disability. For each outcome, the authors constructed an ANCOVA model in which the baseline value of the dependent variable was treated as a covariate while treatment arm	**Depression and treatment outcomes**. The main effect of depression status was not statistically significant on any outcome except for the BPI Interference subscale (p<0.01), which shows a deficit for depressed patients. The estimated effect sizes for depression status were very small to small, ranging from 0.01 for the MOS-SS SOBH subscale to 0.29 for the BPI Interference subscale, with ds<0.17 for the effect of depression status on all remaining outcomes.

Study Details	Patients/Interventions	Methods	Outcomes/Results
Quality Rating: Poor Moderate participation (52.7%) of eligible patients and high attrition (32% did not complete follow-up) although intention-to-treat analysis was performed (method for handling missing data was not reported); potential measurement bias for patients with depression; study lacked adequate statistical power to detect small differences in treatment effects between subgroups; and statistical analysis did not control for important potential confounders		and depression status were treated as fixed factors. **Follow-up:** 12 weeks	No interaction term between treatment arm and depression status reached statistical significance (all p>0.05), and all estimated effect sizes were very small.
Reference: Edlund et al. 2014[6] **Country:** USA **Study Design:** Retrospective cohort study **Purpose: To** investigate the association between exposure to prescription opioids and incident OUDs among individuals with a new episode of a CNCP condition. **Quality Rating:** Fair High participation, low attrition, multivariable analysis adjusted for several (but not all) potential confounders	**Number of Patients:** 568,640 **Diagnosis:** CNCP **Age (Years):** ≥18 years, mean and range not reported **Gender:** 58.3% female **Inclusion Criteria:** The HealthCore dataset included all individuals aged 18 years or older with a new episode of a CNCP condition. Data was from years 2000 to 2005. The following criteria were used to identify new episodes of a CNCP condition: 1) Two or more claims containing primary or secondary diagnoses of the same type of CNCP (back pain, neck pain, headache, arthritis, HIV) that occurred at least 1 month apart but were not separated by more than 1 year; 2) No CNCP diagnoses of the same type in the 6 months prior to the first qualifying diagnosis. Individuals who already had a CNCP condition (e.g. back pain), were eligible for the analytical sample if they had a new episode of a different	The outcome of interest was any diagnosis of an OUD (opioid abuse or dependence) occurring in the 18-month period after the index date. The outcome was binary and derived from ICD-9-CM codes (304.00, 305.50). Opioid daily doses were divided into 4 categories: none, low (1-36 mg), medium (36-120 mg) and high (>120 mg). Opioid days supply was divided into 3 categories: none, acute (1-90 days), and chronic (>90 days). The authors regressed their measure of an OUD on the independent variables in both unadjusted and adjusted logistic regression. Covariates used in the adjusted analyses include opioid dose and days supply, age in years, gender, number of types of tracer pains in the pre-index period, number of non-tracer pain categories, number of non-substance mental health disorder types, pre-index substance abuse/dependence diagnoses, and Charlson score.	**Opioid Dose and Duration**: In a multiple logistic regression, those prescribed opioids had significantly higher OUD rates compared to those not prescribed opioids, and the effect varied by average daily dose and days supply: 1) low dose, acute (OR 3.03, 95% CI=2.32, 3.95, p<0.001); 2) low dose, chronic (OR=14.92, 95% CI: 10.38, 21.46, p<0.001); 3) medium dose, acute (OR 2.80, 95% CI: 2.12, 3.71, p<0.001); 4) medium dose, chronic (OR 28.69, 95% CI: 20.02, 41.13, p<0.001); 5) high dose, acute (OR 3.10 95% CI=1.67, 5.77, p<0.001); and 6) high dose, chronic (OR 122.45, 95% CI: 72.79, 205.99, p<0.001). **Gender and Age**:

Study Details	Patients/Interventions	Methods	Outcomes/Results
	CNCP condition (e.g., headache). Eligible individuals were required to have 12 months of continuous eligibility prior to and 18 months of continuous eligibility after the index date. **Exclusion Criteria:** individuals with OUD diagnoses and/or any prescription opioid use in the 6 months prior to the index date, individuals with a cancer diagnosis at any time in the 12 months before or after 18 months after the index date (other than non-melanoma skin cancer), residents of nursing homes, and those receiving hospice benefits were excluded.	**Follow-up:** 18 months	1) Men had higher rates of OUDs (OR=2.27, 95% CI: 1.85, 2.78, p<0.001), and 2) younger individuals had higher rates than older individuals. For example, the youngest group (ages 18 to 30) had an OR of 10.51 (95% CI=5.47, 20.20, p<0.001), compared to the reference group (age 65+). **Pre-index Mental Health Disorders**: Individuals with pre-index mental health disorders had higher rates of OUDs (OR 3.12, 95% CI: 2.41, 4.04, p<0.001 for those with 1 mental health disorder type vs those with no mental health disorder, and OR=5.71 (95% CI=3.83, 8.52, p<0.001) for those with 2 mental health disorder types vs those with none. **Pre-index Substance Use Disorders**: 1) Individuals with a pre-index alcohol use disorder had a higher likelihood of a post-index OUD (adjusted OR 3.22, 95% CI: 1.79, 5.80, p<0.001) compared to those with no pre-index alcohol use disorder. 2) patients with pre-index non-opioid drug abuse disorders had higher rates of OUDs (OR=8.26, 95% CI=4.74, 14.39, p<0.001) than those without pre-index non-opioid drug abuse disorders.
Reference: Price et al. 2014[7] **Country:** USA **Study Design:** Retrospective cohort study **Purpose:** To describe incident cardiac adverse events and risk factors for cardiac adverse events in primary care patients prescribed methadone for pain. **Quality Rating:** Fair	**Number of Patients:** 1,246 **Diagnosis:** Pain; the group was about equally divided between chronic methadone use and non-chronic methadone use. **Age (Years):** Mean 55.9 (14.4) years **Gender:** 61.3% female **Inclusion Criteria:** Patients were included if they: 1) had purchased one or more methadone prescriptions for pain between January 1, 2010, and December 31, 2010, at a KPCO pharmacy; 2) were 18 years of age or older at the time of purchase; and 3) had continual KPCO membership in the	All patients used methadone for pain relief. Chronic users had a median methadone dose of 30 mg, while non-chronic users had a median dose of 15 mg. A cardiac adverse event was defined as either QTc prolongation ≥500 ms, hospitalization or ED visit without hospitalization for QTc prolongation/TdP, or cardiac death related to methadone use. Multivariate logistical regression modeling was used to determine factors independently associated with having had a cardiac event. Factors tested in the model included age, sex,	**Risk Factors for Cardiac Adverse Events**. Among patients who had a cardiac event and were at risk for an event (n=658), factors independently associated with having had an event included: 1) age (continuous age in years OR 1.06; 95% CI: 1.03-1.09) and 2) methadone doses ≥100 mg/day during follow-up (OR 6.18; 95% CI: 1.08-35.45). No other factors (including concomitant use of QTc prolonging medication) were found to put patients at risk for a cardiac adverse event.